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Archives of Neurology and Psychiatry

VOLUME 31 JANUARY, 1934 NUMBER 1

A STUDY OF APHASIA

THE CHARLES K. MILLS MEMORIAL LECTURE

THEODORE H. WEISENBURG, M.D.

PHILADELPHIA

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INTRODUCTION

Dr. Charles K. Mills, after whom this lecture is named, richly deserved this honor, for in the fifty years of his membership in the American Neurological Association his literary contributions to the scientific advancement of neurology were probably greater than those of any other member. His devotion and loyalty to the association are well shown in the fact that during his long membership he missed only one meeting.

He was fortunate in that his work in neurology began in the golden age of cerebral localization; indeed, the chief contributions to the neurologic literature during his lifetime, particularly in his most active period, were in this field.

Dr. Mills was intensely interested in the problem of aphasia. Twenty-three of his contributions are either directly or to some extent concerned with this subject. He was an extreme localizationist and created many different centers for the various aspects of language. His contribution was important and his influence great.

This research will appear shortly in book form.

Read at the Fifty-Ninth Annual Meeting of the American Neurological Association, Washington, D. C., May 9, 1933.

I remember well the controversy aroused by Marie's views on aphasia. Dr. Mills spent much of his time reexamining the patients with aphasia in the wards for nervous diseases of old Blockley, and at a meeting of the Philadelphia Neurological Society devoted to this subject, he vigorously opposed Marie's views, while Dercum just as vigorously supported Marie. It was a great fight.

With such memories I approach the presentation of the results of my research on aphasia with a great deal of hesitation and humility, but with the hope that the work may have some merit and be worthy of the honor of being presented in the first lecture named after this distinguished scientist.

In the history of neurology there is no subject of greater interest than aphasia. Among its contributors are to be found some of the most distinguished names in neurology. Its development well illustrates the progress of scientific thought, bound by tradition and the forces of dogmatic teaching, but repeatedly advanced by new determinations of fact and the new judgments of independent thinkers.

I should like to discuss enough of the literature to show how the doctrines of aphasia have developed, or at least to place our work in relation to that of other investigators. I am, however, faced with the problem of condensing the results of four years' work into a short report.

As to the literature, I shall refer only to those men whose contributions have been so important that they cannot be entirely overlooked, however brief the discussion. I turn first to two American contributors: Charles K. Mills, with his interest in the structural angle, in the correlation of clinical symptoms with pathologic observations, and in the delimitation of new centers for various language functions, and Adolf Meyer, who, in his Harvey Lecture in 1908, emphasized the importance of careful and complete studies of the patients' responses and outlined a classification of aphasic disorders from the functional point of view.

Of the European investigators, one thinks first of Broca, whose early and striking contributions to the problem of aphasia were so clear and definite that they were at once adopted, and have remained of paramount influence for fifty years. Exactly the opposite was the situation with regard to the views of Hughlings Jackson, whose work is undoubtedly the greatest in the history of aphasia. Jackson's papers were somewhat inaccessible and difficult to read; they were, as Head said, "peppered with explanatory phrases and footnotes," for Jackson was anxious not to overstate his case. Furthermore, he did not accept the misleading simplicity of the explanations current at the time. By detailed observations he became aware of the complexity of the language disorders. He showed that verbal images were not lost, for they came into use again in certain situations, but that the great difficulty was with

speech as propositional expression. A patient could often produce inferior or emotional speech responses when he could not propositionize either internally or externally. In the time at my disposal I cannot do justice to Jackson's views. Suffice it to say that they were comparatively neglected for nearly fifty years, and began to receive their deserved recognition only after Pick's book on "Agrammatism" published in 1913 and Head's work on aphasia.

As to the period following that of Broca and Jackson, I need refer to it only as the age of what Head has termed the "Diagram Makers," when Bastian, Broadbent, Wernicke and others tried to map out various language centers and their interconnections.

These attempts continued and still continue, but they no longer occupy the whole field. They began to lose their position of prominence as early as 1906, when Marie published three papers on the revision of the doctrine of aphasia. He attacked the prevailing views on localization, and he upset current clinical divisions by insisting that the only true aphasia was sensory or Wernicke's aphasia, that pure motor aphasia was what he called anarthria, and that Broca's aphasia was a combination of the true aphasia and anarthria. Furthermore, he contended that every true aphasia involved defect in a special language intelligence and in general intelligence as well.

Since Marie's time there has been a tremendous amount of work on the problem. In general the investigators fall into two groups: those who continue to work from the structural angle, notably Henschen, and those who stress the clinical and, in many cases, the specific psychologic approach. Of the second group, the most prominent are Pick, Head and Goldstein. Each of these investigators has been influenced by Jackson's work; Head particularly has followed closely in Jackson's line of study. Each of them has tried first of all to understand language as a coherent whole, and to make careful analyses not only of speech disturbances, but of the more extensive psychologic changes which appear with the cerebral lesion. Pick is especially noteworthy for his early search for a psychologic explanation of the disturbed language and thinking, Head for his appreciation of the complexity of the language disintegration and his systematic examination of the aphasic patients, and Goldstein for his qualitative analysis of aphasic responses.

Head believed that Jackson was essentially right in his understanding of aphasia as a disorder in propositionizing, but he thought this term ambiguous and substituted for it symbolic formulation and expression. Analysis of his cases, on the basis of results obtained from his serial tests, seemed to him to show four types of disorder of symbolic formulation and expression, which he described as verbal, syntactic, nominal and semantic. His classification thus differs widely from those which

have been generally established. While Head did not believe in a strict localization of speech disorders, he did believe that different areas of destruction in the brain led to these four particular types of disorder of the symbolic process.

His carefully planned serial tests were devised to trace the central disorder of symbolic formulation and expression through its various manifestations in speaking, reading and writing. They are not altogether satisfactory for the study of aphasic disturbances because they do not cover all the performances which must be investigated, and they do not provide for the determination of disturbances of different severity. Furthermore, Head did not make a sufficient study of the results of these tests with nonaphasic and normal persons. In fact, it was the demonstration of this disadvantage that started me in the present research. In 1926, two of my neuropsychiatric students (Pearson and Alpers) were directed to test the other six by Head's tests. The results showed that this supposedly superior intellectual group made some of the same types of errors that aphasic patients made.

Unlike Head, Goldstein has adhered quite closely to the usual classification and differentiated between the "pure" aphasias and the more complicated disorders of a predominantly motor or sensory nature. These he believed to include complex disturbances of inner speech, which, when they appeared alone, constituted a distinct type of disorder, "central" aphasia. Goldstein's work on amnesic aphasia, in which he finds a fundamental disorder of "categorical behavior," has aroused much controversy recently and led to many interesting studies. Pick, Head and Goldstein have all been interested in what has become one of the most widely discussed questions in the modern literature, namely, the mental state of the patient with aphasia and the relation of language to thought.

PLAN OF THE RESEARCH

Through the generosity of the Commonwealth Fund of New York City it was possible to plan a three years' research of the problem of aphasia. The work has actually been in progress for a period of four years. The early part of the first year was devoted to the survey of the literature and the planning of the research. It seemed obvious that little was to be gained by emphasis on the structural side, but this aspect of the work was treated as thoroughly as circumstances permitted. A plan was developed for a psychologic study of the language and other intellectual disturbances consequent on a cerebral lesion. The first problem was the grouping together of adequate test methods which would give a comprehensive picture of such psychologic changes. The tests that were finally chosen, as will be outlined later, are for the most part the mental and achievement tests in common use in schools and

clinics. Similar tests have been used for patients with aphasia before, notably in Germany, but there have been few studies so comprehensive as these, or so complete from the point of view of the analysis of non-language performances. Most of the tests selected had been standardized on children and had been shown to be fairly satisfactory for them from the point of view of validity and reliability.

It was found as the work progressed, however, that some new tests had to be devised, for each individual patient meant a new problem. The specific aphasia study required in addition the selection (1) of tests for which comparable forms could be presented either orally or in print so as to determine the adequacy of the two receptive processes, and (2) of tests which were as nearly as possible tests of comprehension alone, since they required only a simple response such as checking or drawing a line.

There were almost no data on the results of the psychologic and educational tests in adults. It seemed necessary, therefore, to examine a sufficient number to establish the adult performance, and this was done, so that in each instance when I speak of psychologic changes in the aphasic patients it is to be understood that the disturbances are estimated in terms of the normal. This is an important point. So long as there were no adequate studies of normal performances, it was impossible to evaluate the aphasic changes.

Furthermore, it seemed advisable to examine a second type of control patient, a group with cerebral lesions but without aphasia. One group had histories of some speech difficulty.

The number of patients examined, including those with aphasia, normal persons and various other persons used as controls, was 234 (table 1).

Of this total, about 100 showed some aphasia, but only 60 of these were used as the test group for the study of aphasia (table 2).

There were four limitations to the patients selected: (1) The aphasia had to be clearcut, that is, uncomplicated by any other disorder which might lead to changes in mental functioning; (2) the patient had to be under 60 years of age so as to eliminate the question of senility; (3) the mother tongue had to be English; that is, no person was included who first used a foreign language and acquired English secondarily; (4) patients who were blind or deaf were not included.

The patients were obtained from the various hospitals of Philadelphia, the Orthopaedic Hospital and Infirmary for Nervous Diseases, Graduate Hospital of the University of Pennsylvania, Philadelphia General Hospital and some miscellaneous hospitals. Two patients were referred by Dr. Dandy and 1 by Dr. Tilney. Drs. Spiller, Frazier, Winkelman and Flynn, my colleagues in the Orthopaedic, Graduate and Philadelphia General Hospitals and others cooperated by allowing us to study many of their patients.

The normal group of 85 patients was selected from the surgical and orthopedic wards of the hospitals in which most of the aphasic patients were studied. They were comparable to the aphasic patients in age and in educational and occupational groups. This study of the average normal adult is the most detailed that has ever been undertaken, and it will form the basis of a separate publication.

TABLE 1.—*Analysis of Cases*

Total number of cases investigated		314
Total number of patients examined		234
Aphasic patients selected for group	60	
Normal persons	85	
Control patients with cerebral lesions	52	
1. Right hemiplegia, with history of speech difficulty, 10; without, 4	14	
2. Left hemiplegia, without history of speech difficulty	19	
3. Tumors, in right hemisphere, 3; in left, 2	5	
4. Postencephalic parkinsonism	3	
5. Miscellaneous, with aphasic manifestations	11	
Control patients with other neurologic disturbances (multiple sclerosis and tabes dorsalis)	11	
Cases referred by physicians as possibilities for aphasic group but rejected because they did not come within the limitations set (26 of these received detailed examinations)	106	

TABLE 2.—*Analysis of the Aphasic Group*

Type of Aphasia:	
Predominantly expressive	26
Predominantly receptive	17
Expressive-receptive	12
Amnesic	5
Type of Lesion:	
Vascular	37
Tumor	15
Traumatic	8
Race:	
White	50
Colored	10
Age Range:	
12 to 59 years, with a median of 44 years	
Educational Range:	
A year of school through training required for Ph.D. degree, with a median of about 7 years of schooling	
Occupational Status:	
Professional	6
Semiprofessional and business	9
Skilled labor	12
Semiskilled labor	16
Unskilled labor	7
Housewives	7
School boys	3
Class in Hospital:	
Private patients	11
Ward patients	49

The psychologic study of the patients with hemiplegia proved to be very interesting. A word or two will be said about this group later. This particular research is to continue, for it offers many interesting problems.

The following took part in the study: Dr. Bernard J. Alpers made most of the neurologic examinations; Miss Katherine E. McBride organized and had charge of the psychologic work and did most of the

testing of the aphasic patients; Mrs. Mildred Willard Gardiner and Miss Anne Roe did most of the work on the normal subjects and the control group. Without the interest, industry and devotion of this group of workers this work could not have been brought to a successful conclusion.

The principal tests, which are outlined herewith, serve to indicate the extent and the general nature of the disorders.

Outline of Principal Tests

SPEAKING:

Records of spontaneous speech.

Automatic word series: counting; saying days of week and months of year; saying the alphabet; reciting a prayer or a poem.

NAMING:

Standard objects, colors and pictures.

REPEATING:

Words containing all English sounds, and short phrases and sentences.

UNDERSTANDING SPOKEN LANGUAGE:

Response to every-day questions and comments.

Comprehension of words and sentences, as shown by response to the Gates Primary Reading Tests, Types II and III, read aloud to the patient.

Response to Comprehension Tests of Stanford-Binet and Kuhlmann-Binet, and to the Directions of the Head Hand, Ear and Eye Test and the Abelson Geometrical Figures Test.

READING:

Oral: Gates Word Pronunciation Test.
Gray Oral Reading Paragraphs.

Silent: Gates Primary Reading Test.
Chapman Unspeeded Reading—Comprehension Test
Chapman Cook Speed of Reading Test.
Thorndike McCall Reading Scale.

WRITING:

Records of spontaneous writing.

Writing to dictation:
Word dictation: Morrison McCall Spelling Scale.
Sentence dictation: Stanford Achievement Dictation.

Oral spelling: Gates List of Words.

ARITHMETIC:

Computations: Stanford Achievement Arithmetic Computation Test.

Problems: Stanford Achievement Arithmetic Reasoning Test.

LANGUAGE INTELLIGENCE TESTS:

Controlled Association Tests:
Opposites.
Mixed analogies.

Sentence Completion Test: Kelley Trabue Completion Exercises.

Vocabulary:
Oral: Stanford-Binet Vocabulary Test.
Printed: Thorndike Test of Word Knowledge.

REPRODUCTION OF VERBAL MATERIAL:

Reproduction of digit and letter sequences, series of nonsense syllables, disconnected words, sentences and a short story.

NONLANGUAGE TESTS:

Form boards, imitation tests, digit-symbol substitution tests, drawing and picture completions and reconstructions: Pintner Paterson Performance Scale and Pintner Non-Language Mental Test.

DRAWING:

Figures reproduced immediately after presentation.
From model: drawing of a chair.
Drawing of a man scored on the Goodenough Scale.

Rarely would all these tests be necessary in studying changes in mental functioning in any one patient. In most cases those tests were selected for each patient which were within his ability and which were not influenced, or relatively slightly influenced, by any of his specific motor or sensory handicaps. The principal tests may be considered as constituting a preliminary general examination. In outline they perhaps indicate too rigid a method of examination. In practice, aside from the adaptations that have been described, other changes were often necessary. The tests were indeed standard problem situations in which the subject's performance was to be examined, but the determination of the exact nature of that performance was taken to be the chief purpose of the test, so that variations in procedure which would throw light on the nature of the performance were often introduced. These were noted in detail so that the patient's responses could be evaluated and compared, if possible, with those of other patients.

Every response was timed as accurately as possible. Often a comparison of the relative times on different items of a test contributed to an understanding of the nature of the patient's difficulty. The patient's comments were always noted, and whenever he worked aloud, for instance in doing arithmetic, an exact record was made of all that he said. Introspections were often requested, but any attempt at a systematic record was usually impossible, because of the language difficulties, and because the patients were unaccustomed to analyzing their mental processes and expressing the results in verbal terms. Furthermore, the patient's gestures were studied, for he was often able to express by gestures more than he could express verbally.

The length of time spent in the study of each patient ranged from three to ninety-four hours, with an average time of nineteen hours and a median of nine hours. Many of the studies were continued over a long period so that improvement or regression could be studied in detail. Some studies included periods of training as well. The length of the working period was usually an hour, but patients who were easily fatigued worked for shorter periods. An effort was made to see the

patient at the same time each day, and if he thought he did better at any particular time of day, to check his opinion. I hasten to add that for practical work a group of tests has been selected, the application of which need not take more than two and a half hours, and through which it is possible to obtain a fairly accurate conception of the type of aphasia from which the patient suffers.

THE PROBLEM OF CLASSIFICATION

The difficulty of classification is repeatedly demonstrated by the results obtained on the basis of the tests described. When the language process breaks down, the specific disturbances appear in a number of forms of language: speaking, understanding spoken language, reading and grasping the meaning of printed material, writing and so forth. The higher language performances are affected as a result of defects in expressive and receptive functions. Furthermore, these higher language performances may be affected alone, when the expressive and receptive functions are relatively satisfactory. In such an instance the failure, like that of a normal person in a similar situation, is an evidence of inadequate intelligence. This does not mean, however, that the patient is incapable of any high grade mental functioning. He may do very well in performances which demand intelligent behavior but are not directly dependent on language. Another patient may, on the contrary, fail in a variety of language and nonlanguage performances in such a way as to indicate a very extensive change of mental functioning.

It is clear that the term "aphasia," if it is to be preserved as tradition would suggest, must then be understood to include a variety of psychologic changes occurring with a cerebral lesion which are chiefly but not altogether limited to the language process. In a few cases the disorder is apparently confined to language performances; in many, nonlanguage performances are affected to a slighter degree than language performances. In another group, language and nonlanguage performances alike suffer in consequence of a fundamental change in mental functioning.

The proper classification is therefore extremely difficult. Apart from anatomic or physiologic considerations it would be possible to make more than one classification on a purely psychologic basis. An obvious basis presents itself in the form of language most seriously affected: speaking, understanding spoken language, reading and so forth. This grouping would continue the classic types of "aphemia," "word-deafness," "alexia" and "agraphia." These terms have been useful in the past as names for outstanding symptoms. In the course of time, however, they have been generally accepted in the literature and have been used as indicative of definite types of disorder. As such, they invari-

ably mask the true complexity of the aphasic changes. The names are so definite and restricted that they immediately connote some loss in one form of language. Actually such specific loss does not occur. These terms fail to indicate the fundamental relationship of the disturbances or to admit of changes in other language processes. They lead to a simplification which is not in accordance with the facts.

When the language process breaks down, the extremely complicated condition which results is a natural consequence of the complexity of the process as a whole, of the close functional interrelationship of various aspects in the course of their development and of the extent to which language processes have permeated and enriched all mental functioning. The complexity, however, is not without order, and it is on the basis of this observed order that any classification must be made. Groups of disorders cannot be differentiated logically, but must form themselves, as it were, when a sufficient number of cases has been examined in thorough and comparable fashion.

THE CLASSIFICATION ADOPTED

As the aphasic patients were studied it became clear that they fell into three large classes: the predominantly expressive, in which the most serious disturbances were in expression in speech or writing; the predominantly receptive, in which receptive processes suffered more than the expressive, and the changes in speaking and writing were mostly of a different nature from those of the expressive disorder; and the expressive-receptive, in which all language processes were extremely limited. This threefold division was admirable in its simplicity and logic. It did not quite conform to the facts, however, for it required the inclusion within the predominantly expressive group of two different kinds of disorders. On the one hand, there were those patients whose expression in speaking was limited because of defective articulation and formation of words, and in writing because of errors in spelling and gross changes in the formation of the word. These patients, who were handicapped in various degrees by many other disturbances, were the typical expressive patients. On the other hand, there were a smaller number of patients whose expression was disturbed not by defects in the formation of words, but by difficulties in evoking words as names for objects, conditions or qualities. Logically these patients belonged to the predominantly expressive group. Psychologically, however, their disorder was of such a different nature that they could not well be classified with that group. Neither did they belong to the predominantly receptive group, for their understanding remained always relatively superior. A fourth group was therefore created and designated as the amnesic. The term is well established in the literature on aphasia, and it is a satisfactory description of the particular language difficulty.

Every rough division which implies too great a simplification has its disadvantages, and this fourfold division of the aphasic disorders is no exception. It is of practical value only when its disadvantages are thoroughly clear. In the first place, it must be emphasized that none of the terms are other than descriptive, and that none do more than point out the most marked characteristics of the case. Neither the patients of the expressive nor those of the receptive group are handicapped solely in expressive functions, nor solely in receptive. The disorders are only predominantly expressive or receptive; the other processes in either case are always more or less affected, as are language and sometimes nonlanguage performances involving intelligent thinking on a higher level than the specific expressive or receptive functions. Similarly in the amnesic group, while the fundamental difficulty is in the production of words as names, there may be occasional defects in the form of the words produced, and there is always some disturbance in the understanding of spoken language or printed material. Furthermore, although the term "expressive-receptive" is a satisfactory designation for the disorders of that group, it does not indicate the varying degrees of disturbance in the nonlanguage field.

A second disadvantage arises in connection with the receptive disorder. The disturbances of this group include not only limitations in the understanding of spoken language and of printed material, but characteristic defects in expression, confusions in words and grammatical forms and structures which may be very prominent. When they are prominent, the patient's expression in language may be so seriously disturbed that the term "predominantly receptive" is true only by a hair's breadth, or even loses its logical justification altogether. Nevertheless, even if expression is seriously disturbed, the expressive disturbances which consist of verbal and grammatical confusions and the limitations in understanding belong together. They represent one of the principal types of disintegration in the language process. The name to be assigned to them is a minor point, and the term "receptive" has been adopted because the limitations in understanding are almost always more prominent in relation to the disturbances in speaking or writing than is the case in the predominantly expressive disorders.

The Expressive Disorder.—In 26 cases, or 43.3 per cent of the group, the disorders were predominantly expressive. They affected speaking or writing more seriously than the receptive functions. The expressive disturbances were largely defects in the articulation and formation of words in speaking, and changes in the form of the word in writing. In addition to these verbal defects, there were sometimes structural changes consisting of simplification in the sentence or of the omission of words which would have been included in natural

expression. If it were necessary to differentiate the expressive, the receptive and the amnesic disorders on the basis of a single criterion, the nature of the changes in speaking and writing would be that criterion. Disturbances in the articulation and formation of words would be predominant in the expressive disorder, verbal and grammatical confusions in the receptive and difficulties in evoking words as names in the amnesic. At the same time each type would usually be somewhat complicated by the expressive changes characteristic of the other types. The predominantly expressive patient, in addition to his defects in the articulation and formation of words, sometimes has difficulty evoking the correct word as a name and shows occasional verbal and grammatical confusions.

Particularly in the early stages, the expressive patients may be almost speechless. Although they may not speak at all propositionally, they are capable of inferior speech responses, they may swear or make some response as a part of their total reaction to an immediate situation, or they may achieve an automatic performance such as counting.

When speech is less limited and defects in the articulation and formation of words can be studied thoroughly, wide differences become apparent. Some of the expressive patients are more handicapped in the executive mechanisms of language. The normal automatic production of sounds is disturbed, and the patient confuses the sound he is attempting to make, or brings it out only with great effort. In other cases the difficulty is rather in forming the word properly, and attempts sometimes consist of words so garbled as to be quite beyond recognition. Besides the effort required in speaking and the usual retardation, there may also be monotony of the voice and loss of the inflection and accent of normal speech.

The changes in writing generally run closely parallel to those in speaking. Errors in spelling and alterations in the form of the word are analogous to the speech defects in articulation and word formation. Simplified sentence structure and verbal omissions are often prominent in writing, as in speaking. While the changes in the two forms are generally similar in nature and degree, in some cases speaking is much more seriously affected than writing, and in other cases the opposite condition prevails. One of the patients, a woman of 33 years, a typist, showed such a great and specific defect in speaking that she would probably have been classified by many as having subcortical motor aphasia. This patient awoke during the night and found her right side paralyzed and speech impossible; the attack was probably of embolic origin. There were no other symptoms beyond the motor. During the month between the attack and her death, she acquired almost all the speech sounds and could attempt a number of words, which were, how-

ever, always badly articulated. The particular interest of the case was the high quality of her writing, which was apparent even during the first week when she could articulate only a few speech sounds. Writing probably remained fairly satisfactory partly because of her skill in typing. She could write to dictation better than the median of the normal group, but did less well in spontaneous writing. Her errors in spontaneous writing, together with her difficulty in understanding printed paragraphs and the generally poor performances on language intelligence tests, showed that even this case could not be considered as one of specific loss in one form of language, and that here, too, the disorder was actually a complex one.

Another patient, a mechanic of 40 years, illustrates a correspondingly severe loss in writing. His clinical symptoms were indicative of a left motor parietal lesion. He could speak only a few words and could not even write his name correctly. Speech returned more rapidly than writing, so that for several weeks he was able to communicate adequately, if not fully, by speaking, when he still had great difficulty in forming letters in writing and was able to spell only a few words correctly. The change in his writing was severe enough to recall the classic "agraphia," but it was no specific disturbance of one form of language. The patient was extremely confused with any arithmetical problem, and was no more able to construct spatial configurations in drawing than in writing.

The expressive disturbances which have been outlined are only part of the picture. Even in the simpler cases of the predominantly expressive disorder there is some limitation in receptive functions. The limitations may be slight, so that the patients fail only with longer sections or paragraphs or with complicated material. In other cases there are serious receptive disturbances, but not so great as those to be found in patients in the expressive-receptive group.

The quality of the responses to the language intelligence tests varies considerably. Some of the patients' difficulties arise from the fact that their expression in speaking or writing is limited. They can perhaps make an intelligent response by means of gesture when they cannot formulate it verbally. For example, if a patient is asked to give the opposite of the word "crooked," he may be unable to produce the answer either orally or in writing, but he will perhaps draw a crooked line and then a straight line and indicate by gesture that he understands the two concepts. In every case, however, in which one form of expression was at all satisfactory, and consequently adequate studies could be made, there were limitations in the higher language performances beyond those resulting from specific expressive defects.

In comparison with the normal, most patients do relatively better on nonlanguage than on language performances. They can, for instance,

imitate complex movements and complete or construct drawings in such a way as to show a higher level of intelligent behavior than they show in language performances. Rarely, however, is all their nonlanguage work up to the levels which would have been expected before the disorder, and in some cases it shows the same type of change in mental functioning which is manifested in the language defects. The record of a case of expressive disorder will be given later.

The Receptive Disorder.—The receptive group is smaller than the expressive; it numbers 17 patients, or 28.3 per cent of the total. In these cases the predominant disturbances were in receptive functions, but expressive changes were present as well, and were sometimes pronounced. They were of a different nature than the changes in speaking and writing which appear in the predominantly expressive disorder. Defects in the formation of words are less frequent than confusions in the use of words and in grammatical forms. The sentence structure suffers not so much from simplification as from awkward, or actually erroneous, constructions. At the same time the speech is free and fairly easily articulated. Patients of the receptive group often hesitate because they cannot evoke the necessary word with normal ease and speed, but they proceed quickly to substitute another word, right or wrong, or to paraphrase. Their most striking defects, the verbal and grammatical confusions, disturb the quality of their expression, but usually do not limit or retard the actual speaking. If a patient of the expressive group and a patient of the receptive were each to speak in a tongue unfamiliar to the observer, or at such a distance that he could hear the speaking but not understand it, the expressive patient could almost always be distinguished because of one or more of his typical disturbances: retardation, frequent and prolonged hesitations, effort in articulating or changes in the tone and inflection of the voice. In such a situation the receptive patient would usually seem to be speaking normally. He would probably hesitate for words occasionally, and his expression would lack normal continuity and coherence, but the speech itself would issue freely and usually at a normal rate.

The verbal and structural confusions are sometimes as frequent in speaking as in writing, but they are likely to be more pronounced in writing. In both speaking and writing, expressive changes often reveal the tendencies to perseveration and to the contamination of one part of the response by another which are so frequent in the predominantly receptive disorder. A number of the verbal substitutions are similar in meaning to the words which the patient should have used, but many of the verbal and grammatical changes are so complex and variable that they cannot be defined. Their complication and lack of definition repeatedly bear witness to the complexity of the language disintegration. It

is no simple regression along the lines of development; there are few confusions which can be compared with the normal errors at any developmental stage.

Like the defects in expression, which are more extensive in some situations than in others, the limitations in receptive functions are never absolute. Patients can often respond adequately to questions about their own affairs when they are at a loss with other questions objectively no more difficult. In many cases the receptive disturbances are so severe that the patient has difficulty understanding single words and short sentences, and sometimes fails to perceive the word sound accurately. In a few cases the disturbances are comparatively slight, and appear chiefly in the patient's uncertainty with complex directions and in his failure to grasp their full significance.

Limitations in the understanding of spoken language and in the understanding of printed material are usually about equivalent. A few patients, however, experienced far more difficulty in one receptive function than in the other. One of these, a man of 50 years, who had been the manager of an insurance office, showed such great difficulty in all reading processes that he would have been described in the classic terminology as having a case of alexia. The only neurologic symptoms consisted of a slight central weakness of the right side of the face and of a slight increase of reflexes on this side. Psychologic examination showed him to be confused about many letter forms and unable to pronounce most familiar words or to recognize them. His reading disturbances, however, were by no means the only changes, for while his understanding of spoken language was relatively satisfactory, his expression in speech and writing was disturbed by difficulty in evoking the correct words as names and by verbal and structural confusions. This patient's nonlanguage performances were generally high, and it was extremely interesting to find so many of them well executed when the verbal responses accompanying them were so confused.

Nonlanguage performances of good quality are often found in spite of severe verbal confusion; poor performances as a direct result of verbal confusion are on the contrary very rare. On the whole, for the patients of the receptive group, as for those of the expressive group, the nonlanguage performances are superior to the language performances.

The Expressive-Receptive Disorder.—The expressive-receptive group includes 12 patients, or 20 per cent of the total. These cases are set apart from those of the other groups by the severity and extent of the language disturbances. In some, one expressive process or one receptive function is more seriously limited than the other, but on the whole the disturbances are general. Furthermore, they are lasting; the condition is not simply that which may appear in the most severe stages of a disorder, but is a distinct type which may persist through years.

It has been called a "total" aphasia, but that name is not exact, for there is never a complete loss of all signs of language. The limitations in speaking are naturally like those in the most severe cases of expressive disorder, with the greatest disturbance in propositional speaking. Inferior speech responses are sometimes numerous, and are even articulated with ease. A number of patients use some particular phrase at will, and it may be a true speech expression such as "No sir!" or a stereotyped combination of speech sounds. Whatever its nature, it is likely to be produced with a normal inflection and accent. Many patients can swear or utter various phrases arising in emotional excitement or as a part of the total reaction to the situation. Others can count or say some part of another automatic word series.

Expression in writing is not always in proportion to expression in speech. In many it is less extensive, for the inferior forms of emotional or automatic response which make up such a large part of the speech expression appear only rarely as written responses. More or less automatic responses appear in writing, but they are largely confined to the patient's name and perhaps his wife's name or his address. In some of the cases of the group, however, it was clear that writing was less limited than speaking. Several patients who had not been particularly skilled in writing before the disorder could write a number of words when they could produce only a few speech sounds or emotional or automatic phrases. They were accustomed to communicate by means of these written words and supplementary gestures.

When writing was superior to speaking, it was also apparent that the patient understood the printed word somewhat better than he understood spoken words. There were, then, some inequalities within the language processes even in these cases of severe and general limitation. A particularly interesting condition came to light in connection with work in arithmetical computations. These were sometimes comparatively well done; that is, the patient stood higher in relation to the normal group in arithmetic than in any other process directly involving the use of language symbols.

The greatest differences between the patients of the expressive-receptive group, however, appeared in the quality of the nonlanguage performances. As a whole these were always above the language responses, but their superiority was slight in some cases and great in others. Thus, although there is never equivalent deterioration in all performances, there are some instances of rather general deterioration, and others in which there is a great difference between the levels of intelligent behavior as determined by the language and by the nonlanguage tests. In 2 of the cases in which speech was very limited, the nonlanguage performances were far superior to the medians of the normal group, and had obviously suffered little if any deterioration.

The Amnesic Disorder.—The amnesic group includes only 5 cases, or 8.3 per cent of the total. The syndrome is thus comparatively rare, but it is very clear. This is the type of aphasia which has been designated, notably by Mills, as "anomia." The fundamental difficulty in evoking words as names for objects, conditions or qualities leads to serious limitations in speaking and writing and characteristic disturbances in other language performances. The disturbances in expression are quite different from those of the typical expressive disorder. Speech is freely and accurately articulated, but is hesitant and fragmentary because of the words which the patient cannot evoke. Great difficulties appear in all naming tests. It is often evident that the patient has a fairly accurate understanding of the concept when he cannot produce the name as a symbol for it. He can almost always recognize the correct word and select it from a number suggested to him. Furthermore, he is usually very accurate in this selection, and refuses to accept any other than the exact term.

His understanding of spoken language is relatively satisfactory and his understanding of printed material fair. In reading he grasps the meaning of more words than he can pronounce. Apparently the fundamental amnesic disorder makes it difficult for him to produce the word aloud as a name even when he recognizes the printed symbols before him. Writing suffers just as speaking does from the difficulty in evoking the word as a name.

Nonlanguage performances are generally superior to the language performances; but, as in other types of aphasic disorder, it is often evident that the patient does not reach the levels which would have been expected of him originally.

The most interesting amnesic patient of the group was a man of 35, a salesman with a fairly good education, who was studied thoroughly at intervals over a period of two years. When he was first examined he had been having sensory jacksonian convulsions for ten years and had complained of increasing difficulty in finding the words he needed to express his thought, and in remembering such material as telephone numbers.

The neurologic examination was very interesting. Ten years prior to his being seen by me, the patient was studied by another neurologist, and, while at this time he had only sensory jacksonian attacks limited to the right side of the face, he was suspected of having a tumor. In the interval these symptoms increased, and when I first saw him, in addition to sensory fits, there was some slight weakness on the right side. This increased, so that in time a complete right hemiplegia developed. The sensory defects indicated a thalamic lesion. A large infiltrating glioma was partly removed by operation. The patient became gradually worse, and at necropsy the entire temporoparieto-occipital region, practically two thirds of the left cerebral hemisphere, was found to be destroyed.

Repeated psychologic examinations showed that speech was always well articulated, but increasingly scanty and hesitant. The patient used a number of "jumping

off" words, such as "in fact," "of course" or "naturally." He began to have great difficulty in naming objects. Nevertheless, even in the postoperative period, when he could name only about one familiar object of five, he could select the correct name from among several suggested to him. He understood spoken language fairly well, but had more difficulty with printed material. In reading he understood many more printed words than he could pronounce. He could tell, for instance, that the word "son" was "what my mother calls me" and still not be able to say the word "son." His writing, like his speaking, was handicapped by the difficulty in evoking words. Arithmetical performances were interesting because they showed that the patient tried to arrive at the correct sum or product by counting from 1 through the number series; he could not produce the particular number apart from the series.

Cases of amnesic aphasia like this illustrate how extensive the effects of a fundamental language disturbance may be, and how closely interrelated are the various aspects of the language process. At the same time they represent a particular type of language disintegration, different in nature from those more characteristic of the expressive or the receptive disorders. There can be no doubt that aphasia is far from a unitary disturbance; it is simply a convenient name for a rather large group of disorders, some of them apparently confined to the language process and others extending beyond language.

CASES OF GENERAL DETERIORATION AND CONFUSION WITH APHASIA

Eleven patients, not included in the aphasic group, showed aphasic disturbances complicated by various other mental changes. These have been classed as cases of general deterioration and confusion with aphasia. The neurologic diagnoses in these cases were miscellaneous and included suspected tumor of the brain, subarachnoid hemorrhage, Pick's disease, right hemiplegia with cerebrospinal syphilis and generalized arteriosclerosis.

The psychologic changes were extensive and affected the patient's insight and adjustment to social situations as well as his intellectual functioning. Most of the patients were oriented for person, but disoriented for time and place. Many of them spoke somewhat irrationally and incoherently. All of them showed a definite lowering in mental level.

The aphasic phenomena were never more than a part of the picture of general confusion and disorientation. Many patients confused words in speaking, and gave wrong names for objects which they nevertheless recognized. Some produced garbled words in the course of speaking or naming.

They understood simple questions, but their comprehension of more difficult material was uneven, and their attention hard to hold.

Writing was usually more seriously disturbed than speaking, and was particularly faulty in 3 cases in which apraxia was prominent. One

of these patients could produce no more than a scribble; no attempts at letter forms were evident.

Nonlanguage performances were on the whole very poor, and did not show the same superiority to the language performances which was characteristic of the true aphasic groups.

Three patients showed clear apraxia, with severe disturbances in familiar and automatic acts. They could not uncap a pen and start to write without confusing the necessary sequence of the acts. They were likely to strike a cigaret on the match-box and to put the match instead of the cigaret in the mouth. They put their clothes on in the wrong order. Moreover, many of the supposedly automatic movements, such as fastening a pin in a cloth, were carried through very awkwardly, yet there were no peripheral sensorimotor disturbances which would explain this awkwardness. Some of the difficulties these patients experienced seemed to indicate failure to recognize familiar objects, and thus to constitute an agnosic rather than an apraxic disturbance. The finding of apraxic symptoms in these cases is corroborative of the view expressed by von Monakow that such symptoms are indicative of general disturbances of the brain.

Other psychologic changes characteristic of some of the patients of this group were perseveration and the contamination of one part of the response by another, initially good responses with rapid deterioration, disturbances in memory for personal experiences, well known facts and test material, and retardation, hesitancy, monotony or slurring in speech.

REPORT OF THE EXAMINATION OF AN INTERESTING CASE OF PREDOMINANTLY EXPRESSIVE APHASIA

It will be manifestly impossible in the limited time at my disposal to give in detail the psychologic study of any one patient, for, as has been mentioned previously, the average time given to the examination of patients was about nineteen hours.

A short summary of a predominantly expressive case follows:

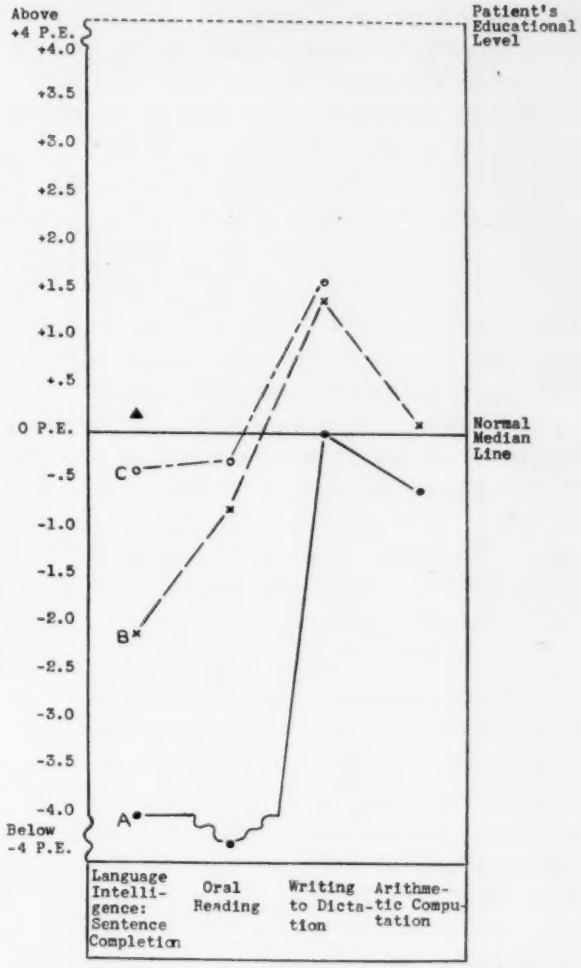
This particular patient, a professor of romance languages at one of the universities, was the most educated and intellectual in the group. For some years he had suffered from hypertension, and about eight weeks prior to his being seen by me he suddenly could not utter a sound. His wife at this time noticed that there was some drooping of the right side of the face. Within half an hour he was unable to use the right arm, and a few hours later the right leg was weak. He probably had a thrombosis of the left middle cerebral artery. The hemiplegia persisted and now he has the usual well marked increase of tonicity in the arm and leg, increased reflexes and Babinski sign with considerable contracture. Sensation had always been normal, and there had been no disturbance of vision. He was right-handed.

Work was carried on with this patient for ten months, during which time he was seen in one hour periods three times a week. He had studied, in the order named, English, German, Greek, Latin, French, Spanish and Italian, old French and Arabic. Apart from English, his mother tongue, he thought that he had been most proficient in Spanish, next in French and then in Italian. German he had known well twenty-five years before, but he had not spoken or written it for that length of time. He read Italian fluently at the time of his attack, but had not conversed for many years. Spanish, French and old French were the languages he was teaching.

The aphasia was predominantly expressive. The initial difficulties in articulation and formation of words gradually disappeared, and the patient became increasingly able to evoke words to express his thought. A year after the attack, however, he was still slow and hesitant in speaking and still below his probable original levels on the language intelligence tests, especially those which demanded the most creative, constructive mental activity. His expression in speech and writing suffered, particularly in the early months, from verbal omissions and simplifications of syntactic structure, and also from occasional verbal and grammatical confusions. His understanding of spoken language and printed material was always far superior to his language expression, but he often failed to grasp the significance of verbal formulations as a whole. Similarly, in other languages and in various nonlanguage performances he was unable to effect a synthesis of a number of parts in a normal intelligent fashion. Some of his poor nonlanguage responses, especially in the drawing completion tests, were not comprehensible in terms of his language disturbance, but were apparently manifestations of the rather general difficulty in constructive mental activity. Other nonlanguage performances, which were largely of a reproductive character, had remained at a relatively high level when language was very inadequate. Thus while most performances, language and nonlanguage, were affected to some extent, the most serious disturbances appeared when the patient had to produce language formulations to express his thought or to construct a coherent whole from given parts.

With regard to the patient's difficulties in foreign languages, it was found that those performances which suffered most in English were also most severely affected in the foreign languages. Spontaneous writing and translation to the foreign tongues were most affected. In each foreign language, as in English, the patient understood far more than he could express. On the whole, the language studies made several points clear: (1) the generality of the disorder which affected all languages; (2) the ranking of the languages from the point of view of qualitative and quantitative superiority in the order the patient himself thought he knew them best: English, Spanish, French, Italian, then classical Latin and German below these. The improvement in these languages seemed to be gradual and no more prominent in one language than in another. In the beginning of the study it was noticed that his speech was monotonous and lacked accent. In view of the fact that his objective was to return to his teaching, this difficulty worried him so much that he had planned to go to France and Spain so that he would recover his usual method of expression. It gradually returned, however, before he had carried out this plan. During the entire period of observation, he was carefully trained. How much his improvement was the result of this work and how much would have returned without it is difficult to say, but there is no doubt that a great deal was the result of training. In fact, he improved so much that in the beginning of the last semester, which was a year after the training had begun, he was allowed to go back to his professional duties, and he has taught successfully about half his usual hours.

The progress which the patient made during his period of training in four representative performances is shown in the accompanying chart. The horizontal center line represents the normal median, and the patient's performances are plotted in terms of their deviation from the normal median for each test. It is evident



Performance levels, no. 4, expressive. Curve *A* is for the first tests, given the third month after the attack; curve *B*, for the second tests, given the fifth month after the attack; curve *C*, for the third tests, given the ninth month after the attack. The black triangle is for the test given in the twelfth month after the attack.

that he was at first very poor in the sentence completion and oral reading tests and much better in writing to dictation. Successive tests showed performances which stood progressively higher in relation to those of the normal group.

THE REGRESSION OF SYMPTOMS

The regression and progression of symptoms are problems of great practical and theoretical importance. By repeated studies, in some cases over periods of two or two and a half years, it was possible to obtain information on the regression of symptoms. Study of the progression of symptoms was rarely possible because few patients were referred until the aphasia had become severe.

There were great differences in the course of the disorder. In some cases there was relatively little change, and the usual severe disturbances of the early period persisted. In others, in which marked improvement took place, it sometimes came rather rapidly, sometimes only gradually. In cases of tumor after successful operative treatment, the improvement was occasionally so rapid that it could not be measured. On one day, for example, the patient would be hesitant and confused in naming objects; on the next day he named them with complete ease and certainty. Within the vascular group there was rarely such rapid improvement, but some patients made great strides in the course of a week. Others changed very gradually, but might continue to improve over a long period. The greatest improvement, however, generally came in the early stages, with progressively smaller amounts of change in the succeeding months. This condition is apparent in the chart. The patient stood higher and higher in relation to the normal group on successive examinations, but the increment was smaller as time progressed.

This case also illustrated another frequent condition, namely, the greater improvement in those performances at first most seriously disturbed. The patient had great difficulty in constructing language formulations, but within twelve months he had improved tremendously in these performances. On the other hand, where he was fairly successful, even at first, there was much less change throughout the succeeding months. When the greatest improvement appeared in those performances at first most seriously disturbed, the disorder as a whole lost its specific character with time.

This loss of the specific character represents one of the changes which may appear in the nature of the disorder. Other changes occur in the early stages when some forms of language may improve more rapidly than others, so that the very general initial disorder may become expressive, receptive or amnesic. Aside from these variations, however, no further changes were observed, even in the patients examined for periods of two or two and a half years; there was no shifting from a disorder of one type to that of another.

APRAXIA AND AGNOSIA

The usual concept of apraxia is expressed in Head's definition: "the loss of power to execute purposive movements or complex acts, in the absence of paralysis and with perfect comprehension of the meaning and ultimate intention of commands, whatever form they may assume." Agnosia is understood as the failure to recognize objects, pictures or sounds when sensory defects which would explain the failure are absent.

Both conditions were originally described by Jackson, and were the subjects of important later work by Pick, Heilbronner and others. In 1900 Liepmann described his famous case and established a doctrine of apraxia which prevailed for many years. It was never uncontested, however; both Pick and von Monakow held views which differed considerably from Liepmann's. Within recent years there have been many attempts to revise the doctrines of both apraxia and agnosia. Particularly significant have been the contributions of Poppelreuter, Goldstein, Kleist and Strauss, Pötzl, Morlàas, Lhermitte, Grünbaum and Sittig.

In the new work there has been the increasingly clearer recognition of the fact that the disorder which is shown depends a great deal on the test methods used, and that some of the differences between cases result from differences in testing. A second important fact now widely recognized is the impossibility of differentiating between the purely motor and the sensory components of any movement. I believe that in every motor action there is always a sensory element, and it is evident, as Pick contended, that the apraxic and agnosic disorders cannot be sharply differentiated from each other. Furthermore, careful study has shown how difficult it sometimes is to make a clear division between apraxia and specific motor defects or between agnosia and specific sensory defects.

The localization of the lesions underlying these disorders is uncertain. Indeed, the pathologic evidence in the literature is such that it is possible to make the stronger statement that the localization has never actually been proved. Many investigators agree with von Monakow that lasting apraxia occurs only with diffuse injuries of the brain. There is a tendency at present, however, to attribute disorders of this type to more limited lesions, which have usually been assigned to the parietal lobe. The anatomic basis for agnosia is generally regarded as extensive, and most of the cases reported have shown bilateral destruction.

Through Liepmann's discussion of aphasic difficulties in motor speech in terms of "apraxia of the speech muscles," the concept of apraxia was greatly extended. A number of investigators considered the defects of motor aphasia as apraxic and the defects of sensory aphasia as agnosic, and a few still hold this view. Particularly since Head's trenchant criticisms, however, aphasic disorders have generally been accepted as of a higher functional order than apraxia or agnosia.

In the comparatively recent literature the concepts of apraxia and agnosia have again been extended, but in a different way. They have come to include disturbances in nonlanguage processes which are characteristic of intelligent thinking. Partly as a result of improved test methods, it has been found that disorders are not limited to defects in simple acts such as grasping or manipulating a familiar object correctly, shaking hands, winking and so forth, but appear in drawing, constructing a figure with blocks, imitating complicated movements and in other types of complex behavior. Following Kleist and Strauss, many of these defects have been included under constructive apraxia. Similarly, in agnosia it has been apparent that defects were not confined to the recognition of familiar objects or sounds, but were sometimes more marked in the appreciation of the significance of a complicated picture or other structure. Visual agnosic defects of this complex variety have been called by Pötzl situation blindness.

Nonlanguage tests such as those used in this study show that both aphasic patients and normal persons differ widely in their success in these performances, for example, in manual dexterity, imitating movements, many types of drawing, perception of form and the understanding of pictures. Members of both groups sometimes make errors which have been described by other authors as apraxic or agnosic. They may, for instance, be unable to draw a simple figure or to interpret a picture. The normal person who makes such errors would not be called apraxic. The aphasic patient who makes similar errors has sometimes been called apraxic in the literature, and yet his failure, when not the indirect result of his language disorder, was, as in the normal person, the result of inadequate intelligence in dealing with certain types of problems.

The questions involved are difficult, and this discussion is merely an outline and is intended as such. It may be said in short that a consideration of the literature and of the results of the nonlanguage tests in this study showed, first, that various defects in complex performances which have been included under apraxia and agnosia are better understood in connection with the larger field of nonlanguage intelligence, and, second, that the concepts of apraxia and agnosia are more useful if they are restricted to defects in relatively simple and more or less automatic responses.

Consequently, the definitions of these terms have been limited. The most satisfactory definition of apraxia seems to be the disturbance in familiar and largely automatic acts such as grasping an object, cutting with scissors and winking. Similarly, the most satisfactory definition of agnosia limits it to disturbances in the recognition of auditory, visual or tactile stimuli for which recognition has become almost automatic.

According to these definitions, it would still be possible to describe executive defects in the production of speech sounds or of letter forms

in writing as apraxic, and defects in the recognition of speech sounds or of letter symbols as agnosic. This is inadvisable, however, because it implies that the disorders of language are limited to disturbances in more or less automatic motor and perceptual responses, whereas all aphasic patients show disorders of language far beyond such limitation.

A number of the aphasic patients had difficulty in taking a given position with the lips, teeth and tongue quite apart from the production of speech sounds. Some, for example, required many trials before they could put the upper teeth against the lower lip as for the sounds f or v. These difficulties are correctly described as apraxic, but they are not infallible criteria for differentiating from the normal because many normal persons are unable to take required positions with the muscles of speech at will.

With the term limited as in the foregoing definition, the only apraxic disturbances shown by the aphasic patients were the occasional defects in taking positions of the lips, teeth and tongue apart from the production of speech sounds. None of the aphasic patients showed any agnosia in the limited sense ascribed to that term. These findings result not only from limitation of the terms, but from the fact that the 60 aphasic patients of the test group had clearcut cases of aphasia, resulting, as nearly as could be determined, from unilateral lesions of the brain and uncomplicated by any other disorder known to affect mental functioning. These cases were chosen to simplify the study of aphasia. Other more complicated cases were examined, and in these there were some instances of apraxia and agnosia. As noted, 3 of the patients in the group with general deterioration and confusion with aphasia showed disturbances in the execution of more or less automatic acts. Two other patients showed apraxia as the result of bilateral lesions. One of these was particularly interesting because her difficulty in handling objects depended to a large extent on inadequate recognition. The comparative rarity of apraxic and agnosic disturbances as defined will be evident from the fact that, with the exception of a few transitory cases, these 5 were the only cases brought to my attention during a survey which has lasted more than three years and during which more than 200 cases of aphasia and other disorders consequent on a cerebral lesion have been investigated.

GENERAL CONCLUSIONS WITH REGARD TO THE CONTROL GROUP OF PATIENTS WITH LEFT HEMIPLEGIA

The group of patients with left hemiplegia were compared first with the normal persons and then with the aphasic patients. It was found that they were far more closely related to the normal persons than to the aphasic patients. They suffered from no specific language disturbances as the aphasic patients did, and in general they showed less

extensive deterioration. There can be no more striking proof of cerebral localization in man than the comparison of a group of patients with left hemiplegia and a group with right hemiplegia, when, of course, both groups are composed of right-handed persons. At the same time, while they showed no disorders comparable to those of the aphasic patients, the hemiplegic patients seemed to have suffered some deterioration. The principal findings, in brief, were as follows:

1. When compared with a similar group of normal persons, the 22 patients with left hemiplegia showed themselves to be inferior in the majority of performances; that is, their median scores fell below the corresponding median scores for the comparable normal group.

2. In a few performances, chiefly in imitating complex series of movements, in following the paths through the Porteus mazes and in solving arithmetical computations, the differences between the medians of the normal group and those of the group with left hemiplegia were great enough to show that the inferiority of the latter was independent of chance factors in the selection of the group.

THE RELATION OF LANGUAGE AND THOUGHT

One of the most fundamental problems in aphasia, as in normal psychology, is that extremely complicated question of the relation of language and thought. The aphasic patients show again and again that there is no parallel between language and thinking. Some patients are able to carry through complex problems outside the language field when they can say only a few words and can understand only the simplest of questions. It may, of course, be contended that their inner speech is more extensive than any articulated or written expression, and this is often true. Nevertheless, there remain patients whose language performances are so limited that any adequate inner speech is hardly conceivable, and who yet compare favorably with the normal group in nonlanguage performances which demand a high level of intelligent behavior. Here we have an illustration of intelligent thinking in spite of extreme language deficit. In another type of case in which language is not limited but is badly confused, there is further evidence that specific verbal formulations are not essential to intelligent thought, for patients of this second type may achieve a good nonlanguage performance when their verbal responses accompanying it are extremely confused. They are not misled by the wrong words; some other terms or images are obviously carrying the right meaning despite the confusion of external speech.

While on the one hand there is this considerable mass of evidence to show that thinking goes beyond language and has no direct relation to it, on the other hand it must be said that in most cases some non-

language performances are inferior to those which would have been expected of the patient before the aphasic disorder. Whether their deterioration depends on the language deterioration or is a distinct phenomenon is a matter which can be settled only for the individual patient in the particular situation. Both conditions occur. There are some instances in which a poor nonlanguage performance seems to depend directly on language inadequacy or confusion. There are others in which both nonlanguage and language performances are affected in a particular way so that a more fundamental change seems to be responsible for disturbances of both types.

Further points of interest with regard to the problem of language and thought arise in connection with the more or less automatic speech responses which some patients produce when they cannot bring forth similar responses at will. Then it is evident that the total situation in which the patient finds himself, bound with some vague intention toward speech response, is sufficient to bring forth this response; that there is here, in other words, something comparable to the automatic speech responses and turns of phrase in the normal person which represent language expression relatively independent of thinking.

Thus it is apparent on the one hand that language may presuppose very little thought, and on the other hand that thinking often extends beyond language formulations. There is no invariable rule, and no determinations can be laid down apart from the particular situation and the individual patient.

LOCALIZATION

In the short time at my disposal it would be impossible to cover the vast amount of literature on this subject. Suffice it to say that the various divisions of aphasia such as motor, sensory, word blindness, word deafness and agraphia have been localized in different parts of the cerebrum. The broad statement can be made that motor aphasia has generally been placed in the region of Broca's convolution and sensory aphasia in the temporal lobe. There has been less unanimity regarding the localization of other syndromes.

Only rarely have there been thorough and complete microscopic examinations in cases in which there has been a satisfactory psychologic study. In this lies part of the failure of the localization.

Several attacks on the problem of localization have been attempted in this study. Only 3 necropsies have so far been obtained, all in cases of tumor. These lesions have been carefully delimited. In 11 other cases of tumor and in 7 traumatic cases, some idea has been gained as to the site and extent of the lesion at the time of operation. It is at once acknowledged, however, that such a localization is inaccurate. In the majority of the patients the lesion was vascular, and, without necrop-

sies, the localization must necessarily depend on the clinical phenomena. Such localization is, of course, not accurate, and any conclusion based on these data must therefore be problematic.

On the preliminary question of localization in the right or left hemisphere, the study presents material from both aphasic and control groups. Analysis of the 98 cases of unilateral cerebral lesion shows:

1. Aphasia or a history of speech difficulty at the time of the attack in 65 of the 67 right-handed patients, with demonstrated lesions of the left hemisphere or neurologic signs of such lesions.

2. Aphasia in 2 left-handed patients, 1 with a demonstrated lesion in the right hemisphere and 1 with a demonstrated lesion in the left.

3. No aphasia or history of it in 22 of the 23 right-handed patients with demonstrated lesions of the right hemisphere or neurologic signs of such lesions.

4. Aphasia in 3 of the 5 ambidextrous patients with a lesion in the left hemisphere, and in the 1 ambidextrous patient with neurologic signs of a lesion in the right hemisphere.

Thus among the 92 clearly right-handed or clearly left-handed patients there are only 4 exceptions to the rule that aphasia appears with lesions of the dominant hemisphere as indicated by handedness, and fails to appear with lesions of the nondominant hemisphere. In other words, the dominance indicated by handedness is a criterion of the crucial hemisphere for speech in about 95 per cent of the cases. As noted, however, there was evidence that language and thought processes were somewhat affected in patients with unilateral lesions which did not lead to aphasia in the generally accepted sense of the word. This condition suggests the close interrelationship of the two hemispheres and the probability that language, while affected most markedly by lesions of the dominant hemisphere, nevertheless depends on the unified functioning of the whole brain.

The localization of the lesions underlying the different types of language disorder as presented clinically is handicapped by the fact that so few necropsies have as yet been obtained. It is unfortunate that there has been no necropsy material in vascular cases. In all probability the results would have been more conclusive than in the cases of tumor. In this regard it is noteworthy that the studies showed the psychologic symptoms to be more variable in the tumor than in the vascular cases. The reason lies in the fact that in the cases of tumor there is nearly always an escape of a certain number of intact axis-cylinders which are capable of functioning.

On the basis of the clinical and pathologic evidence in the vascular, tumor and traumatic cases, it is apparent that in the expressive group the lesion is predominantly in the anterior portion of the brain and to a

less extent in the parietal and temporal lobes. In the receptive cases also the lesion is predominantly in the anterior part of the brain, but to a less extent than in the expressive group, and the implication of the parietal and temporal areas is greater than in the expressive group. Furthermore, there are a few patients of the receptive group who show little or no motor involvement.

In the expressive-receptive group the symptoms point strongly to implication of the anterior part of the brain, but are of little value in indicating the extent to which the lesion involves the posterior areas. Speech and understanding are so limited in patients of this group that sensory examinations are rarely satisfactory. There was evidence of disease of both the anterior and the posterior portions in the 2 cases of tumor in the expressive-receptive group.

In the amnesic type, the lesion in 4 of the 5 cases consisted of a benign, slowly growing glioma in which the involvement was quite extensive, with a varying number of intact axis-cylinders capable of functioning in the infiltrating areas. The case of amnesic aphasia described came to necropsy. There was found a large infiltrating glioma, an astrocytoma, involving the lower half of the precentral and postcentral gyri, almost the whole temporal lobe and the white matter around the inferior and posterior horns of the ventricle on the left side. It is interesting to find these extensive lesions in the amnesic cases in which the language disorders were specific, i. e., consisted of one fundamental difficulty, the evoking of words as names. These cases emphasize the importance of determining the nature of the lesion.

Another attack on the problem of localization has been by selecting those cases in which psychologic examination indicated a preponderant involvement of one language process. These are the cases which in the localization era would have been labeled as cases of anomia, alexia, agraphia and so forth. They consisted of the 5 amnesic cases, 2 cases of preponderant involvement in speaking, 2 in reading, 1 in writing and arithmetic and 1 in writing to dictation. If necropsy material later becomes available, it may be possible to determine why these patients showed a relatively clearer involvement of one language process than did the others of the group. No differentiations can be made on the basis of the clinical findings. Furthermore, in some cases it seems evident that individual characteristics of education and experience are sufficient to explain why there is a preponderant involvement of one language process in a particular case when more extensive disturbances occur in most of the other cases.

It is very much a question whether it will ever be possible to localize from the anatomic standpoint the causes which lead to aphasic disturbances. The disorders in aphasia go beyond speech disturbances, and the complex processes affected depend on the function of the whole brain.

SUMMARY AND CONCLUSIONS

1. A four years' study of aphasia has been completed.

2. The plan of the research was as follows:

To determine the nature and extent of the aphasic changes, a comprehensive group of tests was selected so designed as to cover a wide field of language and mental functioning.

These tests included speech tests, the mental and educational achievement tests in common use in schools and clinics and special examinations devised for particular problems.

In view of the fact that so little was known of adult performances on these tests, they were applied to a group of 85 normal adults comparable to the aphasic patients in ages and in educational, occupational and social classes. The aphasic performances were then estimated in terms of the normal.

Control groups of patients with right and left hemiplegia without aphasia and a group of miscellaneous patients with different types of nervous disease were also examined.

3. Three hundred and fourteen patients in all were investigated, and 234 were examined in detail.

Of this number, 60 aphasic patients were chosen for the study. The criteria for the selection of these patients were: clearcut aphasia, age under 60, English as the mother tongue and adequate sight and hearing.

4. Aphasic disorders never consist of simple losses in one form of language, such as speaking, reading or writing. There is always a more complicated and extensive change, and this is a natural result of the complexity of the language process and the extent to which it has permeated thinking.

5. There are apparent in many cases psychologic changes beyond those which can be explained as a result of the specific language disturbances. The term aphasia must therefore be extended to cover these, and must be understood to represent a group of disorders occurring with the cerebral lesion, the majority but not all of which are changes in the language process.

6. The most satisfactory classification of the aphasic disorders is that based on four divisions: the expressive, the receptive, the expressive-receptive and the amnesic. Of the four, the amnesic represents the only fairly clearcut syndrome. The first three are each descriptive of groups of disorders. Furthermore, the disorders of the first two groups are only predominantly expressive or predominantly receptive; in the expressive there is always some degree of limitation in receptive functions, and in the receptive there are always some defects in speaking and writing.

(*a*) The predominantly expressive disorders handicap speaking and writing more seriously than the receptive functions. They are characterized most obviously by defects in articulation and word formation, but they may involve extensive changes in many language and nonlanguage performances.

(*b*) The predominantly receptive disorders involve relatively serious defects in the understanding of spoken language or of printed material. Expressive disturbances also appear but are almost always less prominent than the receptive; they consist largely of verbal and grammatical confusions.

(*c*) The expressive-receptive disorder is a severe limitation in all language processes, with or without considerable disturbance of nonlanguage performances.

(*d*) The amnesic disorder is a fundamental difficulty in evoking words as names for objects, conditions or qualities and is manifested in many language responses.

7. Within the expressive, the receptive and the expressive-receptive groups there are great differences in the extent of the disorder in individual cases. In some, the relatively simple expressive mechanisms or receptive functions seem to be more disturbed than the higher and more complicated aspects of the language process. In the others, when there is more extensive and proportionate deterioration in all parts of the language process, nonlanguage performances are well preserved in some and considerably disturbed in others.

8. It is apparent that aphasia is not a unitary disorder, but a group of disorders representing different types of disintegration within the language process, and sometimes involving changes in mental functioning beyond the language process.

9. The terms apraxia and agnosia require further definition.

(*a*) Apraxia has been limited to disturbances in familiar and more or less automatic acts which do not depend on sensorimotor defects.

(*b*) Agnosia has been limited to disturbance in the perception of formerly well known objects, forms and sounds, when there are no sensory defects to explain the disturbances.

10. Even with the foregoing limitation, there are two types of apraxia, one involving movements of the muscles of speech, and the other, familiar acts such as manipulating an object and winking. The first type is the only apraxic condition which appeared in the clearcut cases of aphasia. Some of the aphasic patients were unable to take positions of the lips, teeth and tongue at command or by imitation when the production of actual sounds was not in question. The apraxic symptoms of the other type appeared in cases of general deterioration with aphasia or in cases of bilateral lesion.

11. Agnosic disturbances in the recognition of well known sounds, other than speech sounds, of objects or of forms, other than letter symbols, were not found in patients of the aphasic group. In all probability agnosic disturbances as I have defined them do not occur in clearcut cases of aphasia. They may, like the apraxic disturbances of the second type, occur in cases of general or extensive cerebral deterioration.

12. From the standpoint of localization, there is definite evidence of the site and extent of the lesion in the 3 cases in which necropsies have been obtained, and some idea of the localization of the lesions in 11 other cases of tumor and in 7 traumatic cases. Analysis of the side where the lesions appear in relation to handedness shows that the dominance indicated by handedness is a criterion of the crucial hemisphere for speech in about 95 per cent of the cases.

From the clinical symptomatology and pathologic evidence in the expressive cases, the lesions are preponderantly in the anterior portion of the brain and to a less extent in the parietal and temporal zones. In the receptive cases as a group the neurologic symptoms also indicate a preponderant implication of the anterior part of the brain, but less than in the expressive cases and with a greater involvement of the parietal and temporal zones.

In the expressive-receptive cases, the neurologic symptoms point strongly to implication of the anterior part of the brain, but because of the patient's great language difficulties little can be determined about the extent to which the posterior areas are involved.

In all of the cases of the amnesic group the lesions consisted of tumors, 4 of which were large, slowly growing gliomas. These cases emphasized the fact that a relatively specific language disorder can occur with extensive lesions, and pointed to the importance of the nature of the lesion.

I have come to the conclusion that it is not possible definitely to localize aphasic disturbances. As the psychologic studies have shown, language disorders go far beyond the speech process, and I conclude that language is the result of the unified activity of the whole brain.

DISCUSSION

DR. FREDERICK TILNEY, New York: To all of us, and especially to those whose memories run back to the pioneers of the Association, this is an occasion for appreciative reflection. By the establishment of the Charles K. Mills Memorial lectureship, we have enshrined an old and beloved friend. We have put him in his proper niche, not however in the cold features of marble, but in the warm and enduring glow of his aspirations, his achievements and his gallant spirit. It is most fitting that we should do this, for there are very few of us who have not felt directly the influence of his inspiration in one way or another; his indefatigable zeal and enthusiasm, his kindly advice and encouragement have touched each one

of us. Gathering from all parts of the country, we have looked forward each year to seeing him here, and in the long passage of years he seldom disappointed us.

It is not only his friendly kindness and his almost unbroken record of attendance of forty years, his presidency in early manhood and again in our semicentennial year that have endeared him to the Association. He came to our meeting valiantly, always as a leader, often to challenge the unwary adversary and never too enfeebled to defend the faith which he had in the tenets of organic neurology. And now by a wise provision we have assured that he will be with us often as the years pass.

It is also fitting that we have selected as our first lecturer one who is so much in tune with Dr. Mills' spirit, so much in step with his aims. Dr. Weisenburg has long been a virile part of the world renowned Philadelphia school, but, more than that, he has for many years kept a watchful eye over the best interests and development of neurology throughout the country. No member of the Association has contributed more than he toward stimulating growth and maintaining the ideals in our field of medicine. In his recent extensive studies he has made a vigorous frontal attack on aphasia, and now he gives us the results of his investigation, which is probably one of the most comprehensive investigations ever made on this subject.

It is comprehensive not only because of the large amount and variety of clinical material surveyed, but also because of the thorough and extensive methods and controls employed. It takes us far beyond the early conceptions of simplifying schematization, and at the same time it studiously avoids the mist of elaborate hypothesis. One great scientific value which this study has is the manner in which it has kept its eyes on fact and refused to indulge in theories not sufficiently supported by evidence.

The major conclusion that language is the result of the unified activity of the whole brain does not preclude the possibility of exquisite localizations of function within this unit. Neither does it underestimate the implication that the brain as a whole has been operative in animal behavior long before the acquisition of speech, nor does it slight the fact that the cerebrum is active for a long period of development before the slow upbuilding of the speech processes begins. The inference of this conclusion seems clear and also sound. It points to the pervasive nature of the function of language in human behavior which in turn depends on a widespread cooperation in the neuraxis and especially in the brain.

Well considered conservatism is also displayed in the practical diagnostic applications from the facts and from the evidence that receptive, expressive and amnesic disorders in speech have certain definite localizing significance within broad limits.

Wisely enough no attempt was made to circumscribe the functions of speech too specifically, or to write finality in the solution of a problem which has already absorbed so much neurologic effort.

It is my privilege and honor, Dr. Weisenburg, to make this response to your admirable lecture in memory of Dr. Mills. I wish to assure you of my deep and profound appreciation of your splendid work and the lucid and masterly manner in which you have given us the results. In the expression of this appreciation, I am certain that the members of the Association heartily and unanimously join me.

ANALYSIS OF SENSATION IN TERMS OF THE NERVE IMPULSE

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In a previous communication [1] the two groups of fibers in a nerve of the skin associated with touch and pricking pain were identified. The distinctness of the two groups involved lends conclusive support to the theory of specificity of sensory pathways. However, to associate other afferent effects with the specific fiber groups involved in their mediation is not the most cogent purpose in pursuing these studies further. What is needed in this field is a systematization of the phenomena of sensation. Until some unifying system is devised the multiplicity of data and the variety of methods by which they have been accumulated render the physiology of sensation only the more confusing. We believe that these phenomena can be most profitably analyzed where their manifestations are the simplest; not in the skin, where even the character of the sense organs is in dispute, and not in the central nervous system with its manifold complications, but in peripheral nerves where each separate impulse must be manifested as a simple and nonspecific action current in some one afferent fiber. One can set up such impulses in almost any fiber (or group of fibers). One can compare their effects with the effects of stimulating known sense organs in the periphery. One can compare the sensory or reflex effects of applying different known frequencies, in numbers of fibers and combinations of known groups of fibers, with the effects of different stimulating agencies applied to the skin. If, and when, one can synthesize the chief peripheral events of sensation from known impulses in known nerve fibers, one will know what the sense organs must have done to these nerve fibers under any given condition of stimulation to arouse a similar sensation centrally. The nerve impulse may thus be employed as a medium of exchange, a standard in which may be evaluated quantitatively certain aspects of sensation. The central fact, in terms of which we wish to analyze sen-

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1. Heinbecker, P.; Bishop, G. H., and O'Leary, James: Pain and Touch Fibers in Peripheral Nerves, Arch. Neurol. & Psychiat. **29**:771 (April) 1933.

sation,[2] is that any impulse in passing from a highly variable sense organ to a vastly complex sensorium must pass through the stage of the nonspecific nerve impulse in some recognizable nerve fiber; this is the stage at which it can be experimentally interfered with most specifically and with the fewest complications.

In the previous investigation referred to, we observed the sensory effects of stimulating known fibers at known frequencies in peripheral nerves. In a concurrent paper an analysis of the function of the nonmyelinated fibers of the dorsal roots is made (Bishop, Heinbecker and O'Leary [3]). In this communication we present the effects of the blocking of the action currents of known groups of fibers on the sensations mediated from the skin and other peripheral tissues. These effects can be described in terms of partial or total loss of primary sensations with consequent alteration of complex sensory patterns dependent on more than one of them.

HISTORICAL DATA

To render intelligible such a presentation it is necessary to review briefly the development of knowledge of the function of a nerve in relation to sensation. Restrictions of space do not permit adequate recognition of much important work pertinent to the subject, so that of many possible sources a few have been chosen because they appear to indicate best the evolutionary trend.

The older doctrines of the nervous system made no clear distinction between afferent and efferent fibers. Nerve fibers were considered to transmit animal spirits promiscuously, the ultimate effect of which could be either sensation or motion. The first evidence for the functional and structural discreteness of motor and sensory nerves is afforded by the work of Bell [4] and Magendie.[5] Bell established the motor function of the anterior roots. Magendie confirmed Bell's findings as to the function of the anterior roots and established the sensory nature of the posterior roots. Magendie, in his original report, noted that, while the posterior roots are destined particularly for sensation and the anterior roots for motion, they are not exclusively so. However, in the course of time the findings of Bell and Magendie have become incorporated into the so-called Bell-Magendie law, which is usually taken to mean that the

2. Excepting, of course, those more esoteric psychologic qualities which it is not the privilege of the physiologist to evaluate. "Money will not bring happiness," and neither will nerve impulses. It might be argued that both are necessary, but such a sophistication lies beyond the scope of our present methods.

3. Bishop, G. H.; Heinbecker, P., and O'Leary, James: Am. J. Physiol., to be published.

4. Bell, Charles: Idea of a New Anatomy of the Brain, London, Strahan & Preston, 1811.

5. Magendie, Francois: J. de physiol., expér. et path. **2**:276, 1822.

ventral roots of the spinal cord contain only motor fibers and the dorsal roots contain only sensory fibers. The two kinds of fibers may be combined in a single nerve; they are separated only in their connections with the cord. So firmly established has this law become that Bayliss [6] found it necessary to formulate the hypothesis of antidromism to afford an orthodox explanation of definite motor findings for dorsal root fibers.

Next in the evolution of knowledge of the specific nature and function of nerve fibers was Müller's [7] systematization of existing theories of the function of a nerve into the law of specific nerve energies. According to this law, sensation consisted in the communication to the sensorium, not of the quality or state of the external body, but of the condition of the nerves themselves excited by the external cause. Müller stated that "sensation consists in the sensorium receiving through the medium of the nerves, and as a result of the action of an external cause—a knowledge of certain qualities—of the nerves of sense themselves and these qualities of the nerves of sense are in all different, the nerve of each having its own peculiar quality or energy. The nerve of each seems to be capable of one determinate kind of sensation only, and not of those proper to other organs of sense; hence, one nerve of sense cannot take the place and perform the function of the nerve of another sense." He stressed the fact that different kinds of stimuli are capable of arousing nerve fibers, but the result is always specific for each type. The locus of the specific principle, whether it lies in the nerve or in its termination in the brain, was not specifically defined by Müller. It seems certain that he favored the idea that the brain was its seat because of available evidence that the peripheral portion of the nerve was not essential.

Müller's law applied only to the five special senses. Its extension to account for the qualitative differences within a single modality of sense was the work more especially of Natanson [8] and Helmholtz.[9] The latter investigator stressed the indifferent nature of the nerve impulse and argued that the brain only can be the seat of specificity. The ideas of Helmholtz stimulated further search and led to the discovery of sensory skin spots by M. Blix,[10] Goldscheider [11] and Donaldson.[12] As a

6. Bayliss, W. M.: J. Physiol. **26**:173, 1901.

7. Müller, Johannes: Handbuch der Physiologie des Menschen für Vorlesungen, Coblenz, J. Hölscher, 1838, vol. 2.

8. Natanson: Arch. f. Physiol. **3**:515, 1844.

9. von Helmholtz, H. L. F.: Die Lehre von den Tonempfindungen als physiologische Grundlage für die Theorie der Musik, ed. 1, Braunschweig, F. Vieweg & Sohn, 1863.

10. Blix, M.: Ztschr. f. Biol. **21**:145, 1885.

11. Goldscheider, A.: Arch. f. Physiol., 1886, p. 188.

12. Donaldson, H. H.: Mind **10**:399, 1885.

result there was evolved a much more satisfactory classification of cutaneous sensation. Sensibility of the skin was classified under four fundamental modalities, touch, pain, warmth and cold, instead of the previous indeterminate number. Von Frey [13] then correlated different types of nervous receptors in the skin with the four types of cutaneous sensation. This correlation has been disputed, but recently Bazett and his co-workers [14] appear to have produced well founded supporting evidence. The specificity of pain endings is still disputed by Goldscheider, who regards pain as an affective sensory quality, the result of the summation of impulses aroused by intense mechanical stimulation of the sensory endings of both pressure and pain spots.

Investigators of sensory physiology have concerned themselves not only with the fundamental sensory modalities, but also with the problem of explaining those complex sensations experienced in daily contact with the external world and in disease. Many of these sensations represent simply the synthesis of two or more primary sensations. The special quality of others, as experienced in tickling, in the sensation of smoothness and roughness and in other sensations of similar types, according to the work of Thumberg,[15] W. Köhler [16] and von Kries,[17] depends in whole or in part on a stimulus pattern.

The views of von Frey, Goldscheider and von Kries may be regarded as summarizing the status of modern views on sensation before the addition of vacuum tube amplification to physiologic method. Their work left unsettled problems, especially those concerning the nature and function of sensory nerve endings and of sensory fiber groups. Investigations of these particular subjects have recently been undertaken by Adrian and his co-workers in England and by other investigators in America. The bearing of these investigations on those preceding them will be referred to later.

METHOD

It is not necessary to discuss in detail the cathode ray oscillographic technic utilized by us. Elsewhere we have described the manner in which has been deduced a correlation between the form of the conducted action potential of nerve and the

13. von Frey, M.: Ber. d. k. Sachs ges. Wissensch., 1896, p. 23.

14. Bazett, H. C.; McGlone, B.; Williams, R. G., and Lufkin, H. M.: Sensation: I. Depth, Distribution and Probable Identification in the Prepuce of Sensory End-Organs Concerned in Sensations of Temperature and Touch, Arch. Neurol. & Psychiat. **27**:489 (March) 1932. Bazett, H. C., and McGlone, B.: II. The Mode of Cutaneous Sensations of Cold and Warmth, ibid. **27**:1031 (May) 1932; III. Chemical Action in the Stimulation of End-Organ Giving Temperature Sensations, ibid. **28**:71 (July) 1932.

15. Thumberg, T., in Nagel, W. A.: Handbuch der Physiologie des Menschen, Braunschweig, Vieweg & Sohn, 1905, vol. 3, p. 707.

16. Köhler, W.: Jahresb. ü. d. ges. Physiol. **3**:512, 1922.

17. von Kries, Johannes: Allgemeine Sinnesphysiologie, Leipzig, F. C. W. Vogel, 1923.

histologic character of the fiber groups responsible for its components. By gradually increasing the strength of stimulus applied to a nerve trunk still functionally attached in the body, either peripherally or centrally, and simultaneously observing its conducted action potential it is possible to correlate body function with a specific elevation in the nerve's potential complex and thereby also with a specific fiber group. Since the slower conducting potential complexes have higher thresholds than the faster conducting ones, it is possible to isolate, without further differential procedures, the activity only of those fibers responsible for the fastest potential complex. The difference in the threshold of the different fiber groups, however, is appreciable, and, fortunately, the groups are associated with specific changes in body function, which are easily recognizable. It is possible to study the effect of somatic fibers without the complication of the effect of autonomic fibers because of this difference in threshold, and of touch fibers without pain. The technic has obvious limitations which, however, can be obviated by available methods.

There are two agencies which may be employed to block the fibers in a nerve differentially, but in orders which are diametrically opposed. In excised nerves, pressure blocks the larger and more rapidly conducting fibers before the smaller, while cocaine blocks the smaller fibers before the larger (Gasser and Erlanger[18]). Thus, either end of the nerve "spectrum" can be eliminated to leave the other uncomplicated. By means of pressure applied through a constricting band or the gradual closure of a specially designed metal clamp, it is found possible in certain nerves and in certain animals to eliminate the function of the somatic fibers before an appreciable percentage of the slowest fibers, such as the unmyelinated, are affected. This method was utilized to study the function of nonmyelinated fibers uncomplicated by the effects of stimulation of all other fibers. On the other hand, by the application of procaine in spinal anesthesia or in nerve block in animals or in patients, sensory and motor functions can be abolished differentially, beginning with those functions mediated by the fibers of slowest conduction and of highest threshold. Finally, we have made observations on various phases of sensory physiology, utilizing cases exhibiting dissociated sensory loss.

NERVE BLOCK BY PROCAINE IN VITRO

Procaine, from 0.5 to 2 per cent in Ringer's solution, was applied to a short stretch of nerve (0.5 cm.) as it passed through a small glass cylinder between the stimulating and recording electrodes. The nerves employed were mammalian sciatic, saphenous, vagus and cervical sympathetic nerves. More than one kind of nerve was used because the amplitudes of the various potential complexes are much more easily comparable in some nerves than in others. We also wished to ascertain whether procaine was in all essentials comparable to cocaine, which was employed by Gasser and Erlanger in a study of the somatic fibers of peripheral nerves.[18] This proved to be the case. The action potential of the nerve was recorded after from 3 to 5 cm. of conduction. Care was taken to observe the action potential from single as well as from repetitive stimuli, because Wedensky inhibition develops readily on repeated stimulation in depressed nerve fibers. Under the experimental conditions it required from fifteen to twenty-five minutes to block a nerve trunk completely. With fast stimulation the nerve is blocked much earlier, especially its fibers responsible for the two slowest potential complexes.

18. Gasser, H. S., and Erlanger, Joseph: Am. J. Physiol. **88**:581, 1929.

The results in final analysis demonstrated the greater susceptibility to procaine block of the autonomic fibers, which are small, thinly myelinated and non-myelinated, than of somatic fibers (table 1). These autonomic fibers give rise to the two slowest conducting potentials in nerve (B_2 and C). They have a higher threshold and a slower conduction rate than somatic fibers. Wedensky inhibition is a much greater factor in conduction block with stimulation frequencies above from 5 to 10 per second in these fibers than in somatic fibers at a stage showing a corresponding degree of depression of potential amplitude. Since the axon diameter of the myelinated autonomic group is not strikingly different from that of the slowest somatic fibers (from 4 to 1 microns in the cervical sympathetic B_2 groups and from 5 to 1 microns in the saphenous B_1), it is considered probable that the nature of the axons is a factor in determining their differential susceptibility to procaine, as well as their diameter. In the somatic fiber group, which includes the first and second potential complexes (alpha beta gamma and B groups of Erlanger and Gasser, as well as fibers falling in the relative intervals between these groups), the smaller fibers giving rise to the second (B) division are blocked before the alpha beta gamma group. In this larger group the slower fibers are blocked before the faster ones. However, blocking is not complete in

TABLE 1.—*Order of Nerve Fiber Block (in Vitro by 2 per cent Procaine) in Cats and in Saphenous Nerve* *

Time. A. M.	A Wave	B_1 Wave	C Wave
9:00	96	12	7
9:01 (procaine applied)			
9:09	80	4	Absent
9:14	75	1	Absent
9:16	70	Absent	Absent
9:22	55	Absent	Absent
9.45	Absent	Absent	Absent

* The figures denote the maximum heights in millimeters; the amplification was constant throughout the experiment.

the slower somatic group before definite depression, from 30 to 50 per cent, is also present in the faster groups. It therefore can be stated that the order of depression of the fiber is in general in the inverse order of the diameter of the fiber, but that other factors may be involved, such as the character of the axon and the thickness of the myelin sheath. As will be demonstrated later, during spinal anesthesia, motor fibers in motor roots, the maximum diameters of which are larger than those of sensory root fibers, are blocked earlier than sensory fibers in dorsal roots. The myelin sheaths of the sensory root fibers of corresponding size are slightly thicker than those of motor root fibers. A striking feature noticeable on microscopic examination of sections of such motor roots stained with osmic acid is the wide separation of the fibers as compared with those in the sensory roots. This may then be a factor in permitting a readier penetration of the anesthetic. However, in anesthesia of the peripheral nerves motor fibers block before the large sensory ones, so that here we are forced to consider primary the somewhat greater thickness of myelin sheath.

SUBARACHNOID NERVE BLOCK BY PROCAINE

During the course of routine surgical work, spinal anesthesia was administered to six patients utilized for this research. The anesthetic used was procaine crystals dissolved in spinal fluid. The order of sensory and motor loss was followed as the anesthetic became effective and, during recovery, the order of

sensory and motor functional return. Just adequate doses for complete anesthesia were aimed at, and in some cases the sensation of touch was not abolished. The results in all patients studied were remarkably constant, so that a typical experiment as recorded in table 2 is deemed adequate to indicate the results. The changes noted were: first, an increase in the temperature of the skin, after two or three minutes a loss of sensitivity to cold and warmth and then a loss of sensation to pricking pain and pressure pain together. Then there followed a

TABLE 2.—*Sensory and Motor Changes from Subdural Procaine Block (200 Mg.) During Course of Depression and Recovery from Anesthesia* *

Time, P.M.	Touch	Pressure	Joint Sense	Motion	Pricking Pain	Pressure Pain	Warmth	Cold	Comments
3:06	+	+	+	+	+	+	+	+	Plus indicates sensation present
3:09	+	+	+	+	+	+	—	—	Minus indicates sensation absent
3:11	+	+	+	+	—	—	—	—	Depression and return of all sensations gradual
3:12	+	+	+	—	—	—	—	—	Changes in temperature of skin not followed in this case; within first minute 1 C. change is customary; 3 to 5 C. is usual ultimate change
3:15	—	—	—	—	—	—	—	—	
Recovery Phase									
4:04	—	—	—	+	—	—	—	—	Patient could not feel foot move
4:08	+	+	+	+	—	—	—	—	
4:15	+	+	+	+	—	—	—	—	
4:20	+	+	+	+	—	—	—	—	
4:30	+	+	+	+	—	—	—	—	Recovery of touch sensation well advanced; two point discrimination possible and rapidly improved from this point on
4:40	+	+	+	+	+	+	—	—	
4:45	+	+	+	+	+	+	—	—	Hot objects caused pain
4:50	+	+	+	+	+	+	+	+	
4:54	+	+	+	+	+	+	+	+	Hot objects caused burning sensation; with return of temperature sense burning was appreciated; this is different from pain caused by hot object when sense of warmth is absent

* The anesthetic was given at 3:05 p. m.

loss of motor function, and finally a loss of joint sense, pressure sense and sensation of touch in this order, but in close sequence, such that the later sensation was impaired before the earlier was abolished. In recovery the order of return of sensibility was reversed, the gaps between the return of different sensations being much wider. During the return of sensations the ability to localize single stimuli and to recognize two stimulated points as separate went hand in hand with the degree of return of tactile sensation.

BLOCK OF THE PERIPHERAL NERVES BY PROCAINE IN VIVO

While it is regarded by us as certain that spinal anesthesia acts on the root fibers, it might be inferred in opposition to this that the results are in part due to a direct action of the anesthetic on the cells of the spinal cord. To make

certain that conclusions to be drawn from results obtained from observations made on the subjects undergoing spinal anesthesia are justified, the nerves of the skin were blocked in three trained subjects, and the order of disappearance and recovery of sensation was followed. The order was identical with that resulting from spinal anesthesia. The sensation of cold was lost completely before that of warmth, but not before the latter was much depressed.

STUDIES IN A CLINICAL CASE EXHIBITING DISSOCIATED SENSORY LOSS

A colored boy, aged 12, entered the hospital to secure treatment for certain neurotrophic dystrophies involving primarily the skin and subcutaneous tissues. Sensory examination revealed apparently normal touch and pressure sensation. Warmth and cold were well felt everywhere. There was a marked diminution in sensitivity for both pricking and pressure pain. In certain areas these sensations were entirely lost; in others only partly so.

Stimulation of a cutaneous nerve of the forearm was carried out by means of an electrode, shielded except at the tip. This needle was worked through the skin so that its point rested near a nerve of the skin. Thesholds for the various sensations and effects of frequency and of intensity of stimulation were found which determined a normal threshold for tactile sensation when compared with that of other subjects (Heinbecker, Bishop and O'Leary [1]). At a strength of stimulus five times the threshold for tactile sensation, a change in quality of sensation was appreciated and described as pricking, though not painful. Doubling the strength of the stimulus caused only slight pain. At a strength of stimulus from six to seven times that for tactile sensation, a sensation of warmth was experienced which, on stronger stimulation, was described as burning or as a burning pain. The important feature of the result was the appreciation of a sensation of warmth in a subject with a poorly developed sense of pain.

Areas of skin insensitive to pricking pain were tested for their sensitivity to extremes of warmth and cold. A hot metal rod applied to such an area caused a burning sensation. This sensation was said not to be painful in the ordinary sense, but nevertheless was sufficiently unpleasant when applied for a second or more to cause retraction of the arm. A similar hot rod applied to an area in which sensitivity to pricking pain was not lacking resulted in a sensation described as a burning pain, and the reflex effect was decidedly sharper. Freezing the skin of this patient with ethyl chloride in an area insensitive to pricking pain caused only a sensation of wetting and then of cold without pain. No pain was felt on recovery, though some burning was experienced. In areas containing organs of sensitivity for both cold and pain, wetting and cold were the sensations experienced during the process of freezing, but pain was felt on recovery, the sensation being described as a burning pain.

ORDER OF SENSORY LOSS AND OF FIBER BLOCK IN THE PERIPHERAL NERVES

On combining the information derived from the experiments on the in vitro procaine block, subarachnoid and peripheral block anesthesia and the already established correlation between potential form and nerve fiber groups certain conclusions may be drawn. The first fibers to be blocked are the nonmyelinated. These, in the sympathetic

contributions to peripheral nerves, are known to function in vasoconstriction. Their paralysis results in vasodilatation and an increased temperature of the skin. In the dorsal roots similar nonmyelinated fibers prove not to be sensory (Bishop, Heinbecker and O'Leary), but concerned with reflex vasodilatation; the effects of their blocking here are masked by the more pronounced effects of blocking sympathetic fibers. Cold and warmth sensitivity are lost just prior to pain sensitivity. It is therefore considered that the diameter of the fibers mediating these senses are less than those of the pricking pain fibers. The close relationship of temperature fibers to pain fibers, both in depression and during recovery, definitely places them with the latter rather than with the motor fibers governing the caliber of blood vessels. Previous experiments have shown that afferent vasomotor fibers of peripheral nerves are included in the group mediating pain and also, but less numerous, perhaps, in the group mediating touch, but it is not known whether these are nonsensory fibers or whether pain and touch fibers themselves also have a vasomotor influence.

It has been stated that changes in the quality of complex sensations were observed during block as distinct from quantitative loss of primary sensations. In part, these qualitative changes may be assigned to a simplification of the pattern of impulses from a stimulus which activated sense organs of different modalities. In part they may be due to a reduction in the number of pathways available within one modality. For instance, burning pain from a hot object lost its quality of being hot before that of being painful, and finally only touch was recognized. The most obvious effect here was that due to successive failure of impulses over temperature and pain fibers. On the other hand, compass point discrimination failed before touch, apparently merely because some tactile fibers failed before others, and this discrimination is obviously dependent on the frequency distribution of end-organs having accessible pathways to the cortex. More complicated sensory effects, such as wetness and tickle, we are not ready to discuss in these terms further than to state that the few observations we have made appear to suggest similar interpretations.

The foregoing orientation of touch, pain, temperature and motor vasoconstrictor fibers with respect to block by procaine and the correspondence with the successive blocking of fiber groups in excised nerves give us certain points of reference with respect to which fibers mediating other senses may be located in the nerve "spectrum."

Deep pressure sensibility is lost well after pressure pain sensibility during the induction of anesthesia and definitely recovers before pain sensibility. Pressure pain is not perceived until some time after pressure sensibility is well restored on recovery. Pressure pain recovery occurs simultaneously with that of pricking pain. This is interpreted as indi-

cating a similarity of fiber for both pricking and pressure pain. The time relationships of pressure and touch during depression and recovery indicate definitely that the fibers concerned in the mediation of pressure sensibility fall into the group of large fibers associated with touch.

We find no differentiation between fibers for warmth and for burning hot, but there seems to be a fiber difference between hot and pain. A sufficiently uncomfortable sensation can be derived from a hot object to make the subject seek to withdraw from the stimulation at a locus where no pain is felt, but the reflex effect is distinctly less energetic than results from the marked stimulation of pain fibers. When heat stimulation is adequate to injure the skin, the pain fibers are also stimulated, and the resultant sensation is then described as a burning pain.

AFFERENT FIBERS FROM BLOOD VESSELS AND LUNGS

Afferent impulses of a nonsensory type, in that their activity is not associated with conscious awareness, as well as others associated with sensations, such as pain, may result in reflex changes in the caliber of the blood vessels. Such impulses are conveyed typically by the depressor and carotid sinus nerves. The identity of such fibers has been established by stimulating the depressor nerve of rabbits and simultaneously recording the effects on the blood pressure manometrically and the conducted action potential on the cathode ray oscillograph (Heinbecker[19]). It was found that the changes in the blood pressure are initiated by fibers responsible for the first potential of this nerve. These fibers have been shown to be myelinated and of the somatic type, resembling in their various properties the faster of the fibers in the pain group of peripheral nerves and the so-called visceral afferents. No further addition to the degree of change in blood pressure occurs on also stimulating the nonmyelinated fibers of visceral nerves. Similar experiments, previously reported (Heinbecker[19]), have established the fact that myelinated fibers of the somatic type, from 10 to 5 microns or less in diameter, convey the impulses from the lung which modify the activity of the respiratory center. The presence of such nonsenory afferents in these nerves suggests the possibility that fibers in peripheral nerves having similar effects and similar properties may also be distinct from the specifically sensory fibers, even when similarity of physiologic properties permits of no differentiation by our methods.

THE ORDER OF SENSORY RETURN IN REGENERATION OF THE NERVE

Our evidence does not point to such a differentiation between sensory nerve fibers as was suggested by the work of Head, Rivers and Sherren.[20] They postulated a difference between protopathic and epicritic

19. Heinbecker, P.: J. Thoracic Surg. **2**:183, 1932.
20. Head, H. W.; Rivers, H. R., and Sherren, J.: Brain **28**:99. 1905.

pathways. The former was considered to regenerate early and to be concerned with pain and extremes of temperature. Epicritic pathways regenerating later were required as mediating moderate temperature and light touch sensations. That the fibers themselves were considered different by the investigators is evident from their conclusion that the protopathic fibers of the nerve trunk cover a wider area than the epicritic, since after denervation protopathic sensation only is elicited at the margins of the denervated area. It seems more likely that the difference between protopathic and epicritic corresponds to a difference of density of the end-organ which would be manifest owing to overlapping of nerve distribution at the margin of a denervated area, and again within the area as sensory endings are regenerated. Head's hypothesis has received further credibility from the inference that nonmyelinated fibers mediate pain, and there appears the tempting possibility that these fibers, supposedly of primitive histologic type, may prove to be the mediators of primitive physiologic sense. But whatever may be the function of such fibers, it certainly does not correspond to the differentiation supposed to exist, and all the conventional modalities of sensation can be accounted for without them.

With the possibility in mind that different types of nerve pathways might return at different rates after degeneration of a nerve, experiments on degeneration of a nerve have been carried out to determine the rate of regeneration of the different fiber groups in both peripheral and autonomic nerves. No significant difference has been found for the rate of regeneration of the different fiber groups. Within a particular group, fibers of different sizes regenerate at similar rates. If the assignment of all sensory functions to myelinated fibers of the somatic type is correct, the explanation for the earlier return of protopathic as contrasted with epicritic sensibility cannot be found in a differential regeneration of two specific fiber types. If acuity of sensation depends on density of functioning end-organs, the gradual return of sensibility is explained by the fact that a full complement of nerve fibers is not regenerated at one time. Restoration is gradual for all sizes as regeneration of a fiber becomes more and more complete and more and more end-organs are regenerated or connections with them are made. This is what determines the increased acuity of sensation. Differences in the rate of return of the different sensations (pain first, then touch and finally temperature) must depend on differences in the rate of regeneration of end-organs or in the time it takes for functional contact of fibers with their appropriate end-organs. Our evidence does not indicate whether the recovery of touch sensation modifies centrally the affective quality of pain or whether the affective quality of pain is gradually modified during the course of sensory recovery by the functional reestablishment of corticothalamic interrelations.

FUNDAMENTAL MODALITIES OF SENSATION OF THE SKIN

It has been tacitly assumed in the foregoing that the four sensations of the skin—touch, pain, cold and warmth—were primary ones, as has usually been inferred from the fact that these sensations can be evoked by stimulation of single sense organs, and that other sensations were due to various combinations of these. It is also possible, however, to stimulate nerve fibers in nerves of the skin as well as sense organs to produce the same sensations as primary ones, under conditions of differential block, as well as in normal nerve, and in a manner such that the sense organ pattern of the skin is effectively disorganized. We have confirmed Gasser and Erlanger's results with cocaine in finding that procaine blocks fibers differentially with respect to size; and by the fact that the different sensory fibers have different thresholds in vivo, we can confirm from a different angle their inference from results in the literature on narcosis that size is correlated with sense modality. The literature [21] on the order in which these primary sensations are abolished under narcosis is extremely conflicting, and our results do not indicate the order of disappearance which Gasser and Erlanger considered to "receive the strongest support" [22]—pain, cold, warmth, contact. Several factors complicate the determination of the order of disappearance during narcosis when the skin is stimulated.

In the first place the usual anesthetic dose is too concentrated to give accurate differentiation, since anesthesia is too rapid, and it is possible that with a high concentration gradient across the tissue from the site of injection not all fibers of the nerve in question are equally exposed to the narcotic. Second, recovery from anesthesia is more gradual and more differential than induction into anesthesia, and while it takes place as nearly as can be seen in the reverse order of the size

21. In narcosis produced by benzoyl-dimethyl-amino-ethylpropanol hydrochloride, the order of depression, pain, cold, warmth and touch has been reported by Baglioni and Pilotti (Zentralbl. f. Physiol. **23**:869, 1909) and by Thöle (Neurol. Zentralbl. **31**:610, 1912). Goldscheider,[23] utilizing cocaine, found the order to be cold, warmth, pain and touch. Our results, then, agree with those of Goldscheider. Cocaine and procaine have been shown experimentally to affect the fiber groups of excised nerves differentially in the same order. No experiments have been conducted to determine the order of depression under benzoyl-dimethyl-amino-ethylpropanol hydrochloride, but it appears highly improbable to us that the results would differ materially from those obtained under procaine.

22. These authors derive certain inferences as to the correlations of nerve potentials with sensation with which we are not in complete agreement. The discrepancy is, perhaps, accounted for by the fact that they choose their premises as to functional results from a conflicting and, therefore, equivocal literature, without themselves performing such experiments on man or animals. These functional results seem not always to have been derived with the critical acumen with which Gasser and Erlanger performed their own in vitro experiments.

of the fibers it offers a better opportunity for functional test. Third, the area simulated and the intensity of stimulation are factors in the result. When, for instance, the sensation of warmth is abolished and pain is still felt, a stronger stimulus for pain is required than normal, because by this time some pain fibers will have been blocked, and even if not blocked completely will conduct fewer impulses before Wedensky inhibition induced by the anesthetic subvenes on stimulation. We have shown elsewhere that in stimulating nerves directly the intensity of pain felt depends on both the frequency and the number of impulses in a given number of fibers and with a given frequency on the total number of pain fibers activated, that is, on the total number of impulses received centrally. Less than this number of impulses to pain fibers results in a tactile sensation only, as Goldscheider [23] similarly found for stimulation of the end-organs. Finally, one sensation may mask another, especially when the experimental conditions have interfered with the normality of the sensation. With these factors in mind and taking all the precautions that the confusion existing in the literature seems to demand, we have concluded that cold, warmth and pain sensations are blocked by threshold doses of procaine in the order indicated, but that they lie close together in this respect, indicating poor separation with respect to size, the fiber distribution for these sensations overlapping to form one group, the sensory B group.

In subarachnoid anesthesia, besides the temporally successive abolition of sensations over a given area, there occurs a spatial succession of areas in which a differential narcosis is even more instructive. In a case with subarachnoid injection at the lumbar level, for instance, one limb was totally anesthetized in certain areas, and only sensibility to touch was present elsewhere; in the opposite leg sensibility to touch was nowhere completely abolished, and along the abdomen were found successive zones in which further sensations were present even at the maximum state of anesthesia attained. This distribution presumably corresponds to the concentration gradient of anesthetic along the root levels. At the time of maximum anesthesia of the homolateral limb each zone must have been affected by a threshold dose for the particular sensation that was left intact. The spatial order of sensory loss was the same as the temporal, and at the peak of narcosis exhibited a more constant and stable condition for experimental test than did the varying condition during the onset of anesthesia at any one locus.

In the direct stimulation of nerves of the skin no observation of pressure results, It is evident that only the sensation or sensations conveyed

23. Goldscheider, A., in Bethe, A.; Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, p. 131.

by the group of fibers with the lowest threshold can be studied free from the effects of activity in other fiber groups by this method, but it would be expected that an increase of the strength of stimulus would bring into activity successive sensations relatively free from complications of stimulus patterns afforded by end-organs, that is, primary sensations. Such has been found to be the case (Heinbecker, Bishop and O'Leary [1]). The sensation of touch only was experienced when the first group of fibers was activated. On increasing the strength of the stimulus, pain resulted from the activity of a second group of fibers. At the threshold for this group, however, and with infrequent stimulation, only the sensation of touch or of light and nonpainful pricking was reported. Pain is therefore regarded as the affective quality of the pricking sensation, resulting when an adequate number of such impulses reach the central nervous system over a potential pain pathway. Moderate increase of stimulus above the pain threshold results in such intense pain that consciousness could obviously no longer recognize any additional sensory change. Now, while pressure sense is indicated by narcosis to lie in the range of touch fibers, so bland a sensation as touch should not be expected to mask it as pain masks temperature. These considerations indicate that pressure sensation is not mediated by fibers contained in cutaneous nerves, and it is regarded as entirely a deep sensation in the sense that it is mediated by nerves from deeper structures.

The results indicate that sensations of warmth and cold are conveyed by fibers on the average smaller than pain fibers; consequently, in the normal subject one would not expect to obtain a sensation of temperature by direct stimulation of a nerve trunk because of the overwhelming effect of the pain fibers, which would be stimulated first. Our study of the patient showing dissociated sensory loss has afforded evidence of the validity of such an assumption and has demonstrated that if pain can be minimized, owing in our case to an apparent paucity of pain fibers, warmth can be appreciated. The sensation of cold has not been felt on direct stimulation of a nerve of the skin. This would hardly be expected, because our evidence indicates that the sensation of cold is conveyed by fibers even somewhat smaller than those conveying warmth; consequently, both pain and warmth would mask it. That cold is to be regarded as a primary sensation has been adequately demonstrated by Goldscheider and von Frey in their studies on cold spots in the skin and by numerous physiologic and clinical proofs of its separability from the sensation of warmth.

We conclude, therefore, that four primary sensations are mediated by cutaneous nerves—touch, pricking touch, warmth and cold. Pain is the affective quality resulting from a more than threshold stimulation of

a special group of touch fibers, but not from all. Sensations of hot and burning are the affective qualities resulting from intense stimulation of warmth fibers.

FUNDAMENTAL MODALITIES OF DEEP SENSATION

In the course of many surgical procedures carried out under local anesthesia, no evidence of touch sensation from structures beneath the skin has ever been secured. Two sensations only, pressure and pain, are felt by patients on stimulation of such structures. Sensations of warmth or cold from structures beneath the skin are never obtained. One possible exception is noted, namely, a sense of cold or warmth from the stomach on the swallowing of hot or cold liquids, but even here the possibility of transmission of sensations of cold or warmth to the skin is difficult to eliminate. Hot objects applied to the stomach directly in an unanesthetized subject do not result in a sensation of warmth. Results obtained from observations on patients under spinal anesthesia of nerve block have definitely demonstrated that pressure sense is conveyed by fibers in the touch fiber range, whereas pain sense is conveyed by fibers of the same size as are concerned in the mediation of pain from the skin; consequently, there is a pressure pathway independent of pain. Whether pressure pain pathways give sensations of pressure only at the threshold, as the skin pain pathways give a tactile sensation, we cannot say at present. We conclude that two primary deep sensations exist, pressure and (pressure) pain, the difference between these and touch and pain in the skin being primarily differences in end-organs adapted to the stimuli reaching them and in their central connections.

THE RELATION OF THE PROPERTIES OF NERVE FIBERS TO SENSATION

The most precise measure of the nerve impulse at present available is the potential record of its activity. Based on the measurements of the potentials exhibited by different groups of fibers, we have recognized certain differences between two main groups of axons, those innervating typical somatic structures, sensory and motor, and those in the motor autonomic system.

With respect to the division of afferent fibers on the basis of properties correlated with size (the A and B group), it varies from nerve to nerve, but it can be said that pain fibers, visceral or otherwise, fall in the smaller range corresponding to the B group, and that touch and pressure, joint sense and the like fall into the large range, and that many, at least, of the nonsensory afferents, such as respiratory and vasomotor fibers, fall in a middle range which lies between the A and B

waves of such nerves as have these waves well developed. For instance, in the vagus and cervical sympathetic nerves of mammals a potential from fibers with rates of conduction between 35 and 15 meters per second would fall in neither A nor B groups, but would occupy the gap between them. It thus occurs as a fact, whatever the rationale, that the distribution of the potential of any nerve into waves is a reflection of the functions mediated, and the general occurrence of two main potential divisions in the action potential of peripheral nerves may be assigned to the relative absence in these nerves of visceral afferent fibers, resulting in a relative gap in a continuous potential. The significant fact, then, is not the presence or absence of specific waves, but the distribution of potential and a corresponding distribution of fibers according to size in different parts of the continuous range occupied by fibers of afferent function. Histologically, as well as physiologically, the afferent range is potentially continuous and the functional groups overlap.

Adrian [24] has expressed the view that slow fibers with properties which we find characteristic of efferent autonomics are also concerned in the mediation of sensory impulses. We have been unable to confirm these findings. Evidence that the unmyelinated fibers have no afferent function will be presented in detail in another publication.[3] We agree with the dictum of Helmholtz that the impulse in all sensory nerves is essentially the same, with the qualification that the energy content of the individual impulse in the peripheral nerve fibers varies characteristically with the sensation, and that the distribution of similar impulses in time and space within the fibers of a nerve is also characteristic of the whole sensory pathway.

It seems improbable, then, that the character of the individual nerve impulse, which varies from afferent fiber to fiber only quantitatively, is of primary significance in the sensory effect. It is of course possible that the amount of energy delivered per impulse is of significance in a center where synapses may not follow the all-or-none law, but since fibers change their diameters and presumably the energy of their impulses at their terminations, this does not follow as an a priori inference. It seems more probable, however, that the size of fibers has something to do with their vegetative or nutritional function, including in this such matters as the type of end-organ in the periphery that develops about their terminations, or the growth and distribution of their endings in peripheral tissues. This can be only a suggestion, however, prompted by a lack of any other rational explanation of a distribution which is so orderly as to demand some purposive function.

24. Adrian, E. D.: The Mechanism of Nervous Action, Philadelphia, University of Pennsylvania Press, 1932.

THE CONTENT OF THE MESSAGES TRANSMITTED BY AFFERENT NERVE FIBERS

The content of the afferent message in its course through peripheral nerves is obviously made up of nerve impulses, recognizable by their potential manifestations. This content at this level is therefore wholly determined by the character of the nerve fibers involved and by the effect of the sense organs on them, as governing the spatial distribution of the fibers activated and the number and the frequency of the impulses transmitted over them. If we may risk still another generalization in a field where more have been made already than can be correct, a provisional scheme of the peripheral phenomena of sensation may be outlined on the basis of the nerve impulses involved as follows: All fibers mediating superficial sensations of the skin are somatic myelinated ones ranging in size from, say, 15 or more microns down to 1 micron and in conduction rates from 100 meters per second down to 5, and with a threshold range of about 1 to 20, with no important discontinuities in these functions. In the distribution of these fibers in some nerves, two main groups occur, the first of larger size, down to 5 microns, mediating tactile sensations having to do primarily with spatial discrimination, the second of smaller fibers, being concerned with potentially nociceptive sensation. Other afferent fibers in other nerves lie in the range between the main groups found in the nerves of the skin, so that the whole range of fibers is occupied by some known afferent function. The pathways for sensations of the skin may be arranged in the order: tactile, pain, temperature—not only with respect to size of fibers and susceptibility to narcosis, but with respect to other characters. For instance, stimulation of large fibers causes tactile sensation only, of smaller pain fibers only tactile sensation at threshold with a painful affect by summation, and no findings have been reported by any tactile sensation from temperature endings. Stimulation of tactile endings, judging from the results of Adrian, Cattell and Hoagland,[25] as well as from sensory tests, appears to have a brief after-effect; that is, impulses cease in the nerve fibers promptly when the stimulus is removed, and sensation stops abruptly; the sensation is "dead beat." Pain endings in the skin, on the other hand, give a persisting response to the nerve fiber and a persisting sensation, although separate impulses can be felt up to about 60 per second; and while temperature endings or fibers have not been investigated adequately, temperature sensation is notoriously persistent after removal of even a mechanical stimulus. Temperature sensations would seem to be farther removed from tactile in all respects than are pain sensations, even to the extent that temperature sensation does not depend on contact or mechanical energy for its elici-

25. Adrian, E. D.:; Cattell, M., and Hoagland, H.: J. Physiol. **72**:392, 1931.

tation, while pain frequently, at least, results from mechanical contact. Pain lies between touch and temperature in the sense that both contact and heat may affect pain endings; if either deformation or heat was applied to all three types of endings, the threshold for pain would lie between the thresholds for the other two. Whether these relationships have any significance other than to illustrate the vagaries of the rules of chance it is impossible to state, but the order into which these sensory pathways fall seems to be more than a mechanical one, and may have a significance from the developmental standpoint.

Given at least three distinguishable pathways, responses to adequate stimuli differ, then, in the number of impulses set up in the nerve fibers by their respective sense organs (Adrian [24]). These pathways differ again in the effect on their respective centers both of frequency and of the number of impulses in any given fiber, and in the effect of summation of the impulses in more than one fiber serving the same sensation. On direct stimulation of a nerve, increasing the number of touch fibers stimulated mainly increases the area to which sensation is referred, while increasing the number of pain fibers activated definitely increases the amount of pain felt, with poor localization of the area. In fact, increasing the frequency of stimulation in a few fibers and increasing the number of fibers stimulated at the same frequency have very similar results in sensation for pain. We infer that the similarity of sensory effect in the sense organ and in direct stimulation of the nerve indicates a corresponding similarity in the distribution of nerve impulses in these two cases. With this as a basis for sensation, it follows that there are different loci in the central nervous system for reception of different sensations; that is, the character of the sensation is finally determined by the central connections of the different pathways. What we wish to emphasize, however, is that the whole pathway is involved in determining the character of the result, not only the center; while the nerve fibers are relatively nonspecific anatomically, the manner of functioning imposed on them by their sense organs is characteristic to some degree of the sensation to be elicited. The sense organ is more than a device for lowering the threshold to a specific type of stimulus. It also imposes on the nonspecific nerve pathway a characteristic mode of functioning, and this corresponds again to a characteristic type of sensation occurring in the higher centers. The sensory impulse throughout its course is in some degree characteristic of the final sensation produced.

These results afford support for a view that the more complex sensations can be adequately explained as a fusion of simpler or primary ones. With the number of variables that exist, functional as well as anatomic, the permutations and combinations of frequency, fiber group, number of fibers and interrelation of centers offer a good basis for a wide variety of sensation employing a relatively few rather specific types

of pathway. There seems to be no difficulty in reconciling a high degree of specificity of pathways for the primary sensations with the idea that the final sensory effect is also conditioned by the pattern in which peripheral sense organs are stimulated; this pattern, however, includes more than the mere spatial arrangements of the endings in the skin stimulated, that is, the different numbers and frequencies of impulses that any one ending can set up, and the different effects on the center of summation in different pathways; that is, a functional pattern is superposed on the spatial pattern.

SUMMARY

Through direct stimulation of the peripheral nerves and through sensory tests of the skin under stages of narcosis by procaine that produce differential loss of sensations, the nerve fibers have been identified which are responsible for the mediation of the different senses.

On repeating the experiments of Gasser and Erlanger with cocaine, but with substitution of procaine, we confirm their findings that fibers are blocked in the order of size, the smallest fibers first. The corresponding order of sensory loss in narcotic nerve block in vivo is cold, warmth, pain and touch for skin sensation, with vasoconstriction abolished before cold and motor effects to skeletal muscle just before touch. Sensibility to deep pressure and joint sense disappear at the same stage of narcosis as sensibility to touch, and sensibility to deep pain at the same stage as sensibility of superficial pain.

An analysis of sensation in terms of the nerve impulse has been arrived at through studies involving direct stimulation of sensory nerve fibers and studies of narcosis of the nerve fibers produced by procaine.

The experimental evidence supports a theory of specificity of sensory end-organs and demonstrates a specificity of groups of fibers for the fundamental sensory modalities.

Sensibility of the skin consists of four fundamental modalities—touch, pricking touch, warmth and cold. Pain is the affective quality resulting from a more than threshold stimulation of the pricking touch group; hot and burning are the affective qualities resulting from intense stimulation of warmth fibers.

Deep sensibility consists of two fundamental modalities—pressure and pressure pain.

The results afford support for the view that the more complex sensations can be explained as representing a synthesis of the simpler or primary ones. The final sensory effect is also conditioned by the pattern in which the peripheral sense organs are active; this pattern, however, includes more than the mere spatial arrangements of the endings in the skin stimulated, that is, the different numbers and frequencies of

impulses that any one ending can set up, and the different effects on the center of summation in different pathways. A functional pattern is superimposed on a spatial one.

All sensory fibers are myelinated with similar physiologic properties of a type characteristic of somatic nerve fibers. The fibers mediating sensation range in size from 15 or more microns down to 1 micron and in rate of conduction from 100 down to 5 meters per second and with a threshold range of about 1 to 20, with no important discontinuities in these functions. In the distribution of these fibers in peripheral nerves two main groups occur: the first, of larger size down to 5 microns, mediating tactile and pressure sensations, the second, of smaller size, mediating pain and temperature sensations.

Nonsensory afferent fibers conveying impulses governing the reflex control of the caliber of blood vessels and those reflexly modifying respiration are myelinated, with somatic properties. They range in size from 10 down to 3 microns or less and in conduction rate from 35 down to 5 meters per second and have a threshold range of about 1 to 5. They thus fall, according to their properties, in the relative interval between tactile and pain fibers in peripheral nerves.

The intensity of the sensation is a function of the number and frequency of impulses in a single fiber and of the number of active fibers. Modifying influences, aside from psychic ones, are central and peripheral accommodations, and these operate by modifying the number and frequency of nerve impulses received by the sensorium.

Discriminating acuity depends on the number of active end-organs within a given area.

Studies of the regeneration of groups of fibers demonstrate that the different sized groups of sensory fibers regenerate at similar rates. Our results lend no support to Head's theory that epicritic and protopathic sensibilities are conveyed by different groups of fibers.

RÔLE OF THE HYPOTHALAMUS IN REGULATION OF BLOOD PRESSURE

EXPERIMENTAL STUDIES, WITH OBSERVATIONS ON RESPIRATION

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The present investigation was undertaken to obtain adequate evidence either for or against the existence in mammals of a vasomotor mechanism superimposed on the medullary vasomotor center. There is little doubt regarding the existence of a medullary center in the floor of the fourth ventricle through which afferent nervous stimuli and possibly the influences of hormones act. Lately, a center in the hypothalamus has been postulated which would theoretically function as a regulator of blood pressure, acting especially in response to psychic and emotional states. The possible dysfunction of such a center, particularly in an abnormal sensitiveness to psychic or emotional stimuli, could obviously be an important pathogenic factor in the production of clinical "essential" hypertension. In fact, Kahler [1] popularized the concept of a "primary central" type of hypertension due to hyperirritability of a hypothalamic vasomotor center. His evidence, based largely on irregular changes in blood pressure following lumbar puncture in patients with or without hemiplegia due to lesions of the basal ganglia and the adjoining internal capsule, is much weaker than one would suspect from the enthusiastic reception of his theories by some clinicians. The recent publication by Castex [2] of additional clinical evidence of possibly more doubtful value than Kahler's data stimulated us to attack the problem of a hypothalamic center from a strictly physiologic point of view.

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1. Kahler, H.: Ergebn. d. inn. Med. u. Kinderh. **25**:265, 1924.

2. Castex, M. R.: La hipertension arterial hipertonia arterial o hiperpiesis y los estador hipertensivos, hypertónicos o de hiperpiesia, Humberto Andreetta, Buenos Aires, 1929.

PREVIOUS WORK

Probably the first important work concerning superior vasomotor centers was performed by Bochefontaine [3] in 1876 (quoted from von Bechterew). Later, Stricker,[4] in 1886, Francois Franck,[5] in 1888, Cerevkov,[6] in 1892, and von Bechterew [7] himself, in 1881, studied vasomotor effects resulting from cortical stimulation at a time when the cortex was being assiduously charted by electric currents. These workers found a wide area in the frontal, parietal and temporal lobes from which pressor effects could be obtained. They observed so many other apparently localized effects in the vegetative sphere, which have not been confirmed by modern investigations, that it is suggested that the pressor effects they obtained were secondary to some other (perhaps motor) result of cortical stimulation.

The first experimental data concerning elevation of arterial blood pressure on direct stimulation of the hypothalamus (in cats) were furnished by Karplus and Kreidl,[8] in 1909, in their pioneer work on higher sympathetic centers. According to these authors, the effects were not striking, but no definite tracings or figures were presented in their published accounts. However, similar pressor effects (again without details) from stimulation of the floor of the third ventricle were reported by Aschner.[9] In 1918, Karplus and Kreidl [10] stated that electric stimulation of the exposed hypothalamus caused a rise in blood pressure in curarized animals, but that this response was not constantly obtained and was not related to pupillary dilatation or to other phenomena of hypothalamic stimulation. They could not predict when a pressor reaction would be obtained. It was not until 1927 that Karplus and Kreidl [11] published their first graphic record of changes in blood pres-

3. Bochefontaine, L.: Étude expérimentale de l'influence exercée par la faradisation de l'écorce grise du cerveau, Arch. de physiol. normal. et path. **3**:140, 1876.

4. Stricker: Untersuchungen über die Gefässnervencentren im Gehirn und Rückenmark, Med. Jahrb. **1**:1, 1886.

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10. Karplus, J. P., and Kreidl, A.: Arch. f. d. ges. Physiol. **171**:192, 1918.

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sure, which gave meager evidence for their conclusions. They also stated that neither the suprarenals nor the hypophysis was necessary for the rise in arterial pressure produced by hypothalamic stimulation. However, Houssay and Molinelli,[12] using the method of anastomosis between the suprarenal vein of one dog and the jugular vein of another, claimed to have found in the infundibular portion of the third ventricle a center regulating the discharge or secretion of epinephrine. They emphasized the fact that stimulation of the superior part of the fourth ventricle was much more effective in discharging epinephrine than excitation of the hypothalamus. Bard [13] also inferred the presence in the hypothalamus of a center for epinephrine secretion. Karplus [14] stated that the application of a 1 : 1,000 solution of epinephrine to the surface of the exposed hypothalamus, or the injection of the drug into the hypothalamic substance, exerted no pressor effects.

Wang and Richter,[15] in studying the galvanic skin reflex evoked by stimulating the tuber cinereum, stated: "In a series of fifteen animals we were able to confirm Karplus and Kreidl's findings with regard to the pupils, nictitating membranes, lacrimal glands and the general arterial blood pressure." Sachs [16] stimulated many isolated areas of the thalamus (including the hypothalamus), using the Clarke stereotaxic machine, and elicited a variety of respiratory changes, but rises in blood pressure were obtained from certain areas only and then inconstantly. He believed that stimulation of thalamic structures caused changes in respiration and blood pressure only if central sensory fibers were irritated, producing the same effect as irritation of any afferent nerve or pathway converging on the medullary centers. Morgan and Johnson [17] set up chronic irritation of the hypothalamus by injection of a weak solution of corrosive mercuric chloride. They recorded rises in blood pressure; these occurred, however, just preceding or during a generalized epileptiform convulsion.

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12. Houssay, B. A., and Molinelli, E. A.: Compt. rend. Soc. d. biol. **93**:1454, 1925.

13. Bard, P., in The Vegetative Nervous System. Monograph IX, Association for Research in Nervous and Mental Diseases. Baltimore, Williams & Wilkins Company, 1930, p. 167.

14. Karplus, J. P.: Wien. klin. Wchnschr. **43**:622, 1930.

15. Wang, G., and Richter, C. P.: Action Current from the Pad of the Cat's Foot Produced by Stimulation of the Tuber Cinereum, Chinese, J. Physiol. **2**: 279, 1928.

16. Sachs, E.: On the Relation of the Optic Thalamus to Respiration, Circulation, Temperature and the Spleen, J. Exper. Med. **14**:408, 1911.

17. Morgan, L. O., and Johnson, C. A.: Experimental Lesions in the Tuber Cinereum of the Dog Followed by Epileptiform Convulsions and Changes in Blood Chemistry, Arch. Neurol. & Psychiat. **24**:696 (Oct.) 1930; (*b*) ibid., p. 722; (*c*) ibid., p. 709, fig. 4.

In an extensive investigation of the sympathetic nervous pathways involved in the cardiac arrhythmias (chiefly ventricular extrasystoles) occurring during chloroform anesthesia in cats, Beattie, Brow and Long [18] also observed rises in arterial blood pressure during electric stimulation of the posterior portion of the hypothalamus only. They localized the higher sympathetic centers concerned in vasomotor control in an area between the anterior border of the superior colliculus and the mamillary bodies, close to the midline below the thalamic commissure. Recently, Beattie [19] has again placed the control of the sympathetic division of the autonomic nervous system and the nervous regulation of secretion of epinephrine in the posterior part of the hypothalamus.

If the data derived from physiologic experiments on laboratory animals are not sufficiently conclusive to warrant the assumption of a hypothalamic vasomotor center, the natural experiments on man by disease processes are less so. Only a few clinical studies are available. In a remarkable case reported by Penfield [20] of a cholesteatoma periodically obstructing the third ventricle and pressing on the medial anterior and superior aspect of the thalamus on each side, there occurred frequent attacks of "diencephalic autonomic epilepsy" characterized by restlessness, sudden flushing of the skin area supplied by the cervical sympathetic, paroxysmal hypertension (observed only once by chance consecutive readings), lacrimation, sweating, salivation, pupillary dilatation, exophthalmos, tachycardia, slow respiration, pilomotor reflex activity and, rarely, loss of consciousness. The attacks, which usually lasted from five to twelve minutes, would be terminated by a fall in blood pressure, slowing of the pulse, hiccuping, transient "shivering" and Cheyne-Stokes respiration. No suggestion of convulsions was ever seen. The temperature was subnormal during severe attacks. Penfield pointed out that the tumor acted as a ball valve in the foramen of Monro and that the pressure caused by the tumor was above and anterior to the nuclei of the hypothalamus. He concluded that "in the thalamus and not in the hypothalamus lies the highest representation of the vegetative nervous system."

Cushing [21] has drawn on his enormous experience with tumors in the region of the hypophysis and the adjacent base of the brain to

18. Beattie, J.; Brow, F. R., and Long, C. N. H.: (*a*) Physiological and Anatomical Evidence of Nerve Tracts Connecting the Hypothalamus with Spinal Sympathetic Centers, Proc. Roy. Soc., London, s. B., **106**:253, 1930; (*b*) in The Vegetative Nervous System, Monograph IX, Association for Research in Nervous and Mental Diseases, Baltimore, Williams & Wilkins Company, 1930, p. 249.

19. Beattie, J.: Canad. M. A. J. **26**:400, 1932.

20. Penfield, W.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358 (Aug.) 1929.

21. Cushing, H.: Lancet **2**:119, 1930; **2**:175, 1930.

point out that most patients with craniopharyngiomas and compression of the pituitary stalk have "an unaccountably low blood pressure." In only 2 out of 243 patients with large chromophobe adenomas was hypertension found. A normal blood pressure was recorded in a child with a malignant glioblastoma of the chiasma and third ventricle in whom typical "sham rage" occurred.

Most significant of all would seem to be the fact that in Cushing's [22] brilliant experiments on the effects of pituitary and pilocarpine introduced into the lateral ventricle of patients convalescing from intracranial operations, "the expected hemodynamic response has in most cases been surprisingly slight and brief or altogether absent even when the reaction has been otherwise marked." [23] The reaction consisted essentially of marked flushing of the entire skin, excessive sweating, a striking fall in rectal temperature and evidence of increased gastro-intestinal activity —in short, parasympathetic stimulation, which, according to Cushing, was "apparently nuclear in origin and presumably due to diffusion of the substance through the ependymal lining of the ventricle." In a few patients with hydrocephalus and thinning of the walls of the third ventricle or with tumors destroying the walls, no response was obtained to pituitary or pilocarpine.[24] Atropine sulphate given intraventricularly or subcutaneously prior to the introduction of pilocarpine or pituitary prevented the usual general reaction.[25] So also did tribromethanol anesthesia, which is supposed to act on the hypothalamic sleep center.[26] These experiments on man seem to Cushing to support his original theory that the active principle of the neurohypophysis normally passes into the ventricles and acts on the hypothalamic centers. However, the peculiar absence of evidence of stimulation of the hypothetic vasomotor center in the hypothalamus still remains to be explained. Lawrence and Dial[27a] injected pituitary and pilocarpine intraventricularly in dogs. While they obtained results similar in general to those observed by Cushing in human subjects, "it is evident that they are less conclusive and reveal marked differences in the reaction of man and dog. . . ."

No reliable data could be found in the literature to indicate an increased incidence of hypertension in persons suffering from chronic encephalitis, diabetes insipidus, hypothalamic obesity, multiple sclerosis, syphilis of the base of the brain, tumors, or other processes which might conceivably be associated with irritation of the hypothetic hypothalamic

22. Cushing, H.: Proc. Nat. Acad. Sc. (*a*) **17**:163, 1931; (*b*) **17**:171, 1931.

23. Cushing, H.: [22a] p. 168.

24. Cushing, H.: Proc. Nat. Acad. Sc. **17**:239, 1931.

25. Cushing, H.: Proc. Nat. Acad. Sc. **17**:178, 1931.

26. Cushing, H.: Proc. Nat. Acad. Sc. **17**:248, 1931.

27. (*a*) Lawrence, J. H., and Dial, D. E.: Proc. Soc. Exper. Biol. & Med. **30**:49, 1932; (*b*) ibid., p. 54.

vasomotor center. It is well known that destruction of the hypothalamic nuclei produces no clinical symptoms, but this fact is of no value in determining whether those nuclei can regulate vegetative functions. The autonomic nervous system, centrally as well as peripherally, is composed of a somewhat diffuse system of short intercalated neurons forming intricate pathways which it is difficult to map. Destruction of a portion of this system may produce no clinical symptoms because of the accessory pathways of conduction. Irritation of some sort exerting a positive effect through any portion of the system is the only reliable means of investigating localized control of vegetative functions.

METHODS

A. Physiologic.—The experiments were carried out on ninety healthy cats. In two instances dogs were used. The animals were deprived of food for twenty-four hours before the experiments. They were then comfortably fastened to a table and kept warm throughout by means of an electric pad. The hypothalamus was approached in one of three ways: 1. By the original Karplus and Kreidl technic, consisting essentially of a lateral approach for which it was necessary to remove the bone from both lateral aspects of the skull. Bleeding was controlled by bone wax and pieces of muscle. The dura was reflected on one side, and the animal was placed on its back. By this procedure the brain was suspended from the base of the skull. A clear view was obtained of the optic chiasm, the hypothalamus, the oculomotor nerve and the cerebral peduncle. It was easy under direct visualization to introduce an electrode into any portion of the hypothalamus. With the same approach, the cerebral hemisphere on one side could be removed, exposing the lateral region of the hypothalamus. 2. By removing the frontoparietal portions of the skull on both sides, leaving a ridge of bone over the longitudinal sinus, the frontal portions of the hemispheres were exposed. One or both hemispheres could be amputated at the level of the anterior hypothalamus, thus exposing the front surface of the basal regions including the thalamus, subthalamus and hypothalamus. In this and in the preceding method, both common carotid arteries were ligated to reduce hemorrhage. 3. By a transoral technic devised as follows: After reflecting the mucosa, submucosa and periosteum of the posterior end of the hard palate and effecting complete hemostasis and adequate retraction of these tissues and the tongue, a small depression was visible in the midline. From this depression, which is a remnant of the former craniopharyngeal duct, an emissary vein emerges. With a small hand drill this aperture was enlarged down to the dura, which was ruptured by a fine probe, allowing a small amount of cerebrospinal fluid to escape. Electrodes inserted through this opening went through or just behind the hypophysis to enter the hypothalamus. Altering the angle of drilling varied the part of the hypothalamus finally reached by the electrode. It is also possible by this method to enter considerably posterior to the mamillary bodies. Once inserted, the electrode was fastened securely in the mouth and not disturbed.

When stimulation of other parts of the brain, such as the motor cortex or medulla was desired, trephining was done in the appropriate location.

Stimulation: This was effected by faradic electrical current derived usually from three dry cell batteries connected with a du Bois-Reymond inductorium. In some of the earlier experiments, a McIntosh portable induction machine connected

with the alternating current was used to develop a faradic current. In the vast majority of experiments unipolar stimulation was employed, with a large indifferent electrode firmly strapped to the shaven thigh. In a few experiments bipolar stimulation was used. The stimulating electrode consisted either of a fine platinum needle or of a small insulated copper wire sharpened to a point. Care was taken to prevent spread of current. In the case of direct hypothalamic excitation the electrode passed through no other cerebral tissue than the area stimulated. In the experiments with an approach through the oral cavity, the electrodes were kept dry by cotton packing about them so that they did not come into contact with the mucous membrane of the mouth.

The strength of current used varied considerably, but the physiologic stimulus was considered that strength of current which would just elicit contraction from the exposed temporal musculature or could produce a slight tingling sensation on the human tongue. Then the intensity and duration of stimulus were modified during the course of each experiment as shown in the protocols. The length of the stimulus was usually not more than thirty seconds.

Anesthesia: In the early experiments dial was given intraperitoneally in the dose of 0.5 cc. per kilogram of body weight. Apparently negative results with this anesthetic led us to the use of ether inhaled through a tracheal cannula. The depth of ether anesthesia could be easily regulated and controlled.

Curare was administered in the last few experiments. It was given in doses varying from 5 to 20 mg. per kilogram of body weight, well diluted with physiologic solution of sodium chloride and injected subcutaneously, occasionally intraperitoneally or intravenously. The curare was obtained with great difficulty because of its absence from the ordinary markets. Our preparation was purchased from Burroughs-Welcome Company, New York, and consisted of 1/12 grain (0.0054 Gm.) tablets of the drug. During the experiments with curare artificial respiration was instituted, the positive pressure method from an air line connected with the tracheal cannula through a T tube being used. The extent and frequency of inflation were regulated by hand.

Records: The blood pressure was recorded from the common carotid artery by means of a mercury manometer and a kymograph. The anticoagulant was a 5 per cent solution of sodium citrate. Respiration was recorded from a pneumograph strapped to the upper part of the abdomen and connected by air with a small recording tambour. Time was recorded in intervals of five seconds. Accurate observations were made concerning pupillary reactions, muscular movements and other gross phenomena during stimulation.

B. Anatomic.—At the termination of the experiments the brain was carefully removed, sometimes after antemortem intracarotid injection of a 4 per cent solution of formaldehyde. The brain was grossly inspected and the site of the electrode determined, after which a sagittal section was made through the superior longitudinal fissure. The site of the electrode was charted on a diagram. The brain was then cut so that the area from the optic chiasm in front to the cerebral peduncles behind formed one block. From this block serial sections were made in celloidin-embedded material, 15 microns in thickness, and stained with myelin sheath methods and in many cases with cresyl violet. In experiments in which either the rostral or the lateral surfaces of the hypothalamus were exposed and stimulated, several surface sections only were made. The sections were studied, and the position of the electrodes was determined by the hemorrhagic tract in three dimensions and charted on a diagram.

PHYSIOLOGIC RESULTS

A. With Dial Anesthesia and Transfrontoparietal Approach to the Hypothalamus; Both Carotids Ligated (table 1).—In the technically satisfactory experiments in this group, there were five "pressor" animals and one definitely "depressor" cat. In all but cat 4, stimulation was carried out by means of the McIntosh machine, with a current of from 2.5 to 5 volts and unipolar stimulation. The significant feature of the pressor effects on stimulation of the hypothalamus was their almost

TABLE 1.—*Typical Effects of Hypothalamic Stimulation in Cats of Group A: Karplus and Kreidl Approach to Hypothalamus, Dial Anesthesia*

Cat	Strength of Stimulus	Duration of Stimulus	Body Movements	Blood Pressure, Mm. Hg: Control	Blood Pressure, Mm. Hg: During Stimulation	Blood Pressure, Mm. Hg: After Stimulation	Respiration	Anatomic Site of Stimulation
4	4 cm.*	Short	++	86	124	84	Present	Posterior medial part of hypothalamus
	4 cm.	Short	++	84	188	140	Apnea	Posterior medial part of hypothalamus
	6 cm.	Short	++	80	150	118	Present	Posterior medial part of hypothalamus
	7 cm.	Short	0	74	82	78	Present	Posterior medial part of hypothalamus
7	5 volts†	16 sec.	0	124	144	126	Present	Section made through pars
	5 volts	14 sec.	0	126	154	124	Present	preoptica hypothalamus;
	5 volts	20 sec.	0	114	150	114	Present	stimulation of posterior
	5 volts	8 sec.	0	116	130	116	Present	part of hypothalamus extending into periaqueductal region of midbrain
8	7.5 volts	5 sec.	+++	132	150	120	?‡	In midbrain beneath posterior commissure; also
	5 volts	5 sec.	++	120	158	116	?	posterior part of
	2.5 volts	10 sec.	0	128	142	112	?	hypothalamus
	2.5 volts	15 sec.	++	118	168	118	?	
9	5 volts	3 sec.	++	93	78	106	?	Hypothalamus and subthalamus, numerous
	5 volts	5 sec.	++	94	78	106	?	areas
	5 volts	3 sec.	++++	92	72	100	?	
12	5 volts	2 sec.	++	138	144	130	?	Hypothalamus thoroughly
	5 volts	4 sec.	++	128	110	128	?	explored with electrode
	2.5 volts	8 sec.	++	116	140	92	?	

* Coil distance.
† McIntosh machine, faradic current.
‡ Respiration not observed.

invariable association with muscular movements and respiratory changes. As to the actual rise in blood pressure with varying strengths of stimuli introduced into all possible areas in the hypothalamus, the maximum increase was 50 mm. in all but cat 4, in which rises as high as 104 mm. were obtained from the induced current from dry cell batteries, with the secondary coil at a distance of only from 4 to 6 cm. to produce effects. This is a powerful stimulus. However, with the secondary coil at 6, 7 and 8 cm. no effect was elicited. In cat 8, on stimulating area 9, which extended into the midbrain from the subthalamus, there were no movements with a current of 2.5 volts, which produced a rise of 14 mm. of blood pressure. When repeated, the same current failed to produce any significant effects. In cat 7, pressor effects ranging from 14 to

TABLE 2.—*Representative Experiments to Illustrate Effects of Stimulation of the Hypothalamus or Other Parts of the Brain in Cats of Group B; Hypothalamus Approached Through Mouth; Ether Anesthesia*

Cat	Strength of Stimulus (Coil Distance), Cm.	Duration of Stimulus, Sec.	Body Movements	Degree of Anesthesia	Blood Pressure			Respiration	Anatomic Site of Stimulation
					Before, Mm. of Mercury	During, Mm. of Mercury	After, Mm. of Mercury		
19	10	10	0	Light	100	80	100	?	Medulla
	5	45	0	Deep	104	150	100	?	Medulla
	4 to 7	10 to 50	0	Light		No effects		?	Posterior part of hypothalamus
24	9	15	++++	Light	98	116	90	Apnea	Medial part of hypothalamus, in third ventricle
	10	15	+	Light	92	94	92	Slowed	Medial part of hypothalamus, in third ventricle
	8	15	++++	Light	94	120	82	Apnea	Medial part of hypothalamus, in third ventricle
27	6 to 12	20 to 35	0	Deep		No effects		No effect	Anterior hypothalamus
	6	15	++++	Light	118	138	80	Apnea	Anterior hypothalamus
	9	20	+++	Moderately deep	140	142	140	Apnea	Anterior hypothalamus
	8	22	+++	Moderately deep	140	149	128	Apnea	Anterior hypothalamus
28	5 to 11	10 to 20	0	Moderately deep		No effects		No effect	Center of hyopthalamus (medially)
	4	7	++++	Moderately deep	142	170	102	Apnea	Center of hypothalamus (medially)
	9	10	+	Moderately deep	100	108	96	Slowed	Left motor cortex
	10	10	±	Moderately deep	100	102	100	No effect	Left motor cortex
	8	20	++++	Moderately deep	92	112	90	Apnea	Left motor cortex
	9	10	+++	Moderately deep	84	88	84	Apnea	Midline cerebellum toward medulla
	8	12	++++	Moderately deep	92	110	64	Apnea	Midline cerebellum toward medulla
	8	18	++++	Light	55	82	50	Apnea	Midline cerebellum toward medulla
29	10	18	+	Deep	160	168	156	Slowed	Posterior medial part of hypothalamus
	9	15	++	Deep	148	164	134	Apnea	Posterior medial part of hypothalamus
	8	24	+++	Deep	140	160	106	Apnea	Posterior medfal part of hypothalamus
	6	26	++++	Deep	122	188	86	Apnea	Posterior medial part of hypothalamus

30	11 to 5	7 to 10	0	Light		No effects		No effect	Posterior medial part of hypothalamus
	4.0	30	±	Light	110	115	110	Slight apnea	Posterior medial part of hypothalamus
	3.5	10	++++	Light	110	154	80	Apnea	Posterior medial part of hyopthalamus
	4.0	10	++	Light		No effects		Apnea	Left motor cortex
	3.5	5	++++	Light	72	82	60	Apnea	Left motor cortex
	2.5	15	++++	Light	64	110	40	Apnea	Left motor cortex
32	9	20	++	Light	126	132	124	Apnea	Left motor cortex; (1) before destruction of
	8	11	++++	Light	118	138	102	Apnea	right posterior part of hypothalamus
	8	25	++++	Light	132	160	96	Apnea	
	9	28	++	Light	120	128	112	Slowed	(2) After destruction of hypothalamus
33	9	10	++	Moderately deep	204	206-186	196	Slowed	Left motor cortex
	8	5	+++	Moderately deep	204	164	156-196	Apnea	Left motor cortex
	9	12	++	Moderately deep		No effects		Slowed	Hypothalamus
	8	8	++++	Moderately deep	186	212	136-172	Apnea	Hypothalamus
	8	10	++++	Moderately deep	170	198	138-166	Apnea	Left motor cortex again
	10	12	±	Moderately deep		No effects		No effect	Both cortex and hypothalamus
	8	9	++++	Moderately deep	180	196	126-158	Apnea	Both cortex and hypothalamus
	10 to 4	5 to 10	0	Moderately deep		No effects		No effect	Hypothalamus destroyed, cortex stimulated
	3	12	++	Moderately deep	180	188-160	142-172	Apnea	Hypothalamus destroyed, cortex stimulated
	7	4	++++	Moderately deep	160	214	102-132	Apnea	Hypothalamus stimulated
34	10 to 6	10 to 15	0	Light		No effects		No effect	Posterior part of hypothalamus
	3	6	++++	Light	118	178	80	Apnea	Posterior part of hypothalamus
	4	1% mercuric chloride injected into hypothalamus				No effects		Arrhythmia	Posterior part of hypothalamus
	6	8	++++	Light	98	106	74	Apnea	Posterior part of hypothalamus
36	10	28	+	Light	114	124	120	Increased	Posterior part of hypothalamus
	9	22	++	Light	138	150	124	Slight apnea	Posterior part of hypothalamus
	8	14	++	Moderately deep	144	154	140	Increased	Proximal sciatic nerve
	8	11	++	Moderately deep	116	134	114	Increased	Proximal sciatic nerve
	8.5	8	++	Moderately deep	118	130	96-110	Slowed	Hypothalamus again
47	12	8	0	Light		No effects		No effect	Posterior part of hypothalamus, extending to
	10	15	±	Light	136	140	128	Unchanged	midbrain
	9	12	++	Light	134	144	130	Slowed	
	8	9	+++	Light	148	156	124-140	Apnea	After destruction of hypothalamus
	9	10	Slight	Moderately deep	136	138	124	Slowed	
	8	12	+++	Moderately deep	124	132	102-118	Apnea	
	7	13	++++	Moderately deep	130	168	76-88	Apnea	

TABLE 3.—*Comparative Effects of Stimulation of Anterior and Posterior Hypothalamus, of the Cerebral Peduncle, and of Other Parts of the Brain in Cats of Group C; Karplus and Kreidl Approach to Hypothalamus; Ether Anesthesia*

Cat	Strength of Stimulus (Coil Distance), Cm.	Duration of Stimulus, Sec.	Body Movements	Degree of Anesthesia	Blood Pressure			Respiration	Anatomic Site of Stimulation (After left hemidecerebration)
					Before, Mm. of Mercury	During, Mm. of Mercury	After, Mm. of Mercury		
45	10	3	±	Moderately deep	94	...	88	Increased	Anterior part of hyopthalamus
	10	5	±	Light	92	96	88	Slowed	Posterior part of hypothalamus
	10	6	++	Light	92	78	90	Slowed	Brain stem
	8	5	+++	Moderately deep	86	70	66-80	Apnea	Residual cortex
	10	8	++	Moderately deep	80	84	70	Slowed	Dorsal part of thalamus
	8	5	++++	Moderately deep	72	103	52-62	Apnea	Hypothalamus
50	10	10	±	Very light		No effects		Slowed	Surface of hypothalamus
	9	10	+	Very light	112	108	112	Slowed	Anterior part of hypothalamus
	9	5	+	Very light	100	104	100	Slowed	Posterior part of hypothalmus
	9	10	+	Light	130	142	120	Apnea	Lateral part of hyopthalamus
	9	20	++	Light	118	152	108	Apnea	Lateral part of hypothalamus
51	10	20	+	Moderately deep	80	80	80	Slowed	Lateral part of hypothalamus
	10	20	+++	Light	85	88-72	68	Apnea	Lateral part of hypothalamus
	9	16	+++	Moderately deep	105	108-88	82-96	Increased	Lateral part of hypothalamus
	9	16	+++	Light	84	64	56-70	Slowed	Lateral part of hypothalamus
	9	15	+++	Light	74	58	55-71	Apnea	Posterior part of hypothalamus
	9	30	+++	Light	79	71	79	Slowed	Motor cortex
52	11	10	+	Light	149	154	154	Slowed	Anterolateral hypothalamus
	11	18	+	Moderately deep	180	180	180	Slowed	Anterolateral hypothalamus
	10	21	+	Moderately deep	180	183-173	181	Slowed	Anterolateral hypothalamus
	9	26	+++	Moderately deep	184	186-161	182	Apnea	Anterolateral hypothalamus
	10	23	+	Moderately deep	182	178	175	Slowed	Posterior part of hypothalamus
	9	21	+++	Moderately deep	175	161	155-166	Apnea	Posterior part of hypothalamus
	9	31	+++	Moderately deep	160	161-136	150	Slowed	Posterior part of hypothalamus near peduncle
	8	18	+++	Moderately deep	150	161	99-130	Apnea	Peduncle
	10	31	+	Moderately deep	147	146	141	Slowed	Third ventricle
	9	23	+++	Moderately deep	141	134	133-125	Apnea	Third ventricle
	10	13	+	Moderately deep	84	74	84	Tachypnea	Posterior part of hypothalamus (after left hemidecerebration)
	10	33	+	Moderately deep	80	86	79	Slowed	Posterior part of hypothalamus (after left hemidecerebration)
	9	25	+++	Moderately deep	81	83	68-75	Slowed	Posterior part of hypothalamus (after left hemidecerebration)
	10	18	0	Moderately deep	75	79	73	Slowed	Anterior part of hypothalamus (after left hemidecerebration)

58	11	12	0	Light	100	100	100	Increased	Anterior part of hypothalamus
	10.5	3	++	Light	108	109	108	Apnea	Anterior part of hypothalamus
	11	25	+	Light	116	116	116	Increased	Posterior part of hypothalamus
	11	22	+++	Light	104	146	92-130	Slowed	Left peduncle
	11	27	++	Moderately deep	112	120	108	Slowed	Left peduncle
	11	25	++	Moderately deep	118	122	118	Increased	Midhypothalamus
	10	24	+++	Moderately deep	106	120	90	Apnea	Anterior part of hypothalamus
	10	20	+++	Moderately deep	120	142	96-132	Apnea	Left peduncle
	10	30	++	Moderately deep	124	140	103-128	Apnea	Anterior part of hypothalamus
	12	24	0	Moderately deep	140	148	122-136	No change	Left peduncle
	12	15	+	Moderately deep	118	124	102-116	Slight change	Anterior part of hypothalamus
	12	15	+	Moderately deep	118	124	102-116	Slowed	Posterior part of hypothalamus
	13	25	0	Light	122	116	112	Increased	Left peduncle
	13	18	+	Light	116	124	114	No effect	Anterior part of hypothalamus
	13	16	0	Light	118	118	118	No effect	Anterior part of hypothalamus
	12	15	++	Light	118	146	92-116	Apnea	Left peduncle
	12	24	±	Moderately deep	114	116	106	Apnea	Left peduncle
	12	18	0	Moderately deep	112	114	112	Apnea	Anterior part of hypothalamus
	9	11	++++	Moderately deep	116	158	82-100	Apnea	Left peduncle
	9	17	++	Moderately deep	112	118	104	Apnea	Anterior part of hypothalamus
64	12	21	++	Light	145	190	152	Increased	Anterior part of hypothalamus
	12	29	+	Moderately deep	181	186	186	Apnea	Anterior part of hypothalamus
	11	38	++	Light	164	182	161	Increased	Anterior part of hypothalamus
	11	22	++	Moderately deep	156	166	139-158	Slowed	Posterior part of hypothalamus
	11	16	0	Moderately deep	158	160-154	159	Slowed	Posterior part of hypothalamus
	10	36	+	Light	160	178-153	146-168	Increased	Posterior part of hypothalamus
	11	18	+++	Moderately deep	164	185	120-163	Slowed	Left peduncle
	12	36	+	Moderately deep	160	172	151	Slowed	Left peduncle
	10	25	+++	Moderately deep	158	183	135-149	Apnea	Left peduncle
65	12	28	++	Light	126	131	129	Slowed	Anterior part of hypothalamus
	12	30	+	Light	127	125	114	Slowed	Posterior part of hypothalamus
	12	23	+	Light	106	115	93	Slowed	Midhypothalamus
	12	23	++	Light	101	160	98-109	Apnea	Left peduncle
66	12	29	++	Light	153	162-132	118-144	Slowed	Anterior part of hypothalamus
	12	40	++	Light	141	146-129	131	Increased	Lateral wall of hypothalamus
	12	36	++	Light	134	139-118	118	Slowed	Posterior part of hypothalamus
	11	60	++	Light	129	145-117	110	Increased	Posterior part of hypothalamus
	12	40	+++	Very light	99	118	94	Apnea	Peduncle
67	12	40	++	Light	160	170-144	139-156	Slowed	Anterior part of hypothalamus
	10	35	++	Moderately deep	164	180-150	166	Apnea	Anterior part of hypothalamus
	10	30	0	Deep	170	174-160	167	Slowed	Anterior part of hypothalamus
	12	36	++	Light	136	146-130	144-132	Slowed	Posterior part of hypothalamus
	10	45	++	Very light	145	160-128-166	134	Apnea	Posterior part of hypothalamus
	9	22	+++	Moderately deep	146	198	142	Apnea	Posterior part of hypothalamus
	12	25	++	Moderately deep	152	178	134-158	Slowed	Left peduncle
	10	22	++	Moderately deep	168	184-148	176	Slowed	Motor cortex
	6	20	++++	Moderately deep	166	224	130-140	Apnea	Motor cortex

TABLE 3.—*Comparative Effects of Stimulation of Anterior and Posterior Hypothalamus, of the Cerebral Peduncle, and of Other Parts of the Brain in Cats of Group C; Karplus and Kreidl Approach to Hypothalamus; Ether Anesthesia—Continued*

Cat	Strength of Stimulus (Coil Distance), Cm.	Duration of Stimulus, Sec.	Body Movements	Degree of Anesthesia	Blood Pressure			Respiration	Anatomic Site of Stimulation
					Before, Mm. of Mercury	During, Mm. of Mercury	After, Mm. of Mercury		
67-a	12	1	+ (head)	Very light	121	130	108	Slowed	Anterior part of hypothalamus
	12	30	++	Light	116	126	100-112	Increased	Middle part of hypothalamus
	12	57	++	Light	120	140	118	Increased	Middle part of hypothalamus
	9	15	0	Moderately deep	140	144	140	Increased	Middle part of hypothalamus
	8	20	++++	Moderately deep	140	186	150	Apnea	Middle part of hypothalamus
	12	62	++	Light	130	178	110-128	Apnea	Posterior part of hypothalamus
	12	50	++	Deep	130	134	130	Hyperpnea	Posterior part of hypothalamus
	8	20	++++	Deep	120	140	84-112	Apnea	Posterior part of hypothalamus
69	12	20	+	Very light	112	140-108	126	Slowed	Anterior part of hypothalamus
	12	27	+	Very light	96	88-96	80	Slowed	Posterior part of hypothalamus
70	12	41	+ T*	Light	179	177	168	Slowed	Anterior part of hypothalamus
	11	61	++ T	Light	171	212-204	164-183	Slowed	Anterior part of hypothalamus
	11	47	++	Light	188	217	180-190	Slowed	Anterior part of hypothalamus
	11	30	+	Deep	178	178	178	Slowed	Anterior part of hypothalamus
	12	56	+	Moderately deep	114	132	110	?	Anterior part of hypothalamus
	10	70	+++	Moderately deep	108	164-120	...	.....	Anterior part of hypothalamus
71	12	45	++	Light	135	138	135	Slowed	Anterior part of hypothalamus
	9	38	+++	Light	144	160	126-154	Apnea	Anterior part of hypothalamus
	9	15	0	Deep		No effects		.....	Anterior part of hypothalamus
	8	30	+++	Deep	135	160	122-132	Apnea	Anterior part of hypothalamus
	10	36	++++	Deep	134	157	123	Apnea	Posterior part of hypothalamus
	8	55	++++	Deep	129	161	119	Apnea	Posterior part of hypothalamus
73	12	25	+++	Very light	84	96	76	Slowed	Middle part of hypothalamus
	9	40	+++	Light	104	114	80	Slowed	Middle part of hypothalamus
	9	55	+++	Light	90	108-88	76	Apnea	Middle part of hypothalamus
	9	55	+++	Very light	90	110	78-90	Apnea	Middle part of hypothalamus
	13	25	0	Very light		No effects		.....	Middle part of hypothalamus
	11	23	++	Very light	96	104	100	Slowed	Middle part of hypothalamus
	9	55	+++	Very light	96	112	82	Apnea	Middle part of hypothalamus
74	12	45	0	Light		No effects		Slight increase	
	11	30	++	Light	162	156	159	Slowed	Posterior lateral part of hypothalamus
	10	24	++	Light	159	150	158	Slowed	Posterior lateral part of hypothalamus
	9	25	+++	Light	156	164-150	135-148	Apnea	Posterior lateral part of hypothalamus
	8	26	++++	Light	154	172-150	110-148	Apnea	Posterior lateral part of hypothalamus
76	11	25	+	Light	80	76	66-78	Hyperpnea	Left lateral midhypothalamus
	10	16	+	Light	75	83	61-72	Hyperpnea	Left lateral midhypothalamus
	9	30	+++	Light	69	86	61-74	Hyperpnea	Left lateral midhypothalamus
	9	24	+	Deep	66	71	64	Slowed	Left lateral midhypothalamus
	8	30	+++	Deep	69	75-61	57-61	Hyperpnea	Left lateral midhypothalamus
	8	30	+++	Moderately deep	61	81	57-61	Hyperpnea	Left lateral midhypothalamus

* T = tonic movements.

36 mm. of mercury were also obtained in the absence of muscular movements. These results followed stimulation of the midline of the hypothalamus posteriorly; they were less marked from the anterior part of the hypothalamus. Cat 9 was a depressor animal which consistently showed a primary fall, followed by a secondary rise in blood pressure, on electric stimulation sufficiently strong to produce body movements. This effect was obtained from widely different areas, such as the hypothalamus, subthalamus and thalamus. The maximum fall in blood pressure was 20 mm. of mercury, and the greatest secondary rise was 13 mm. It is interesting that this animal, a depressor preparation, and cat 4, which gave the maximal pressor effect of this series, had initial blood pressure levels ranging from 80 to 90 mm. of mercury, which is relatively low in comparison with the blood pressure of other animals. In none of these cats was respiration graphically recorded, but our notes indicate that apnea occurred during many of the more vigorous stimulations.

B. Ether Anesthesia; Hypothalamus Approached Through the Mouth (table 2).—In this series, from cat 24 to cat 49 inclusive, and including cat 19, all possible variations in effects on blood pressure were obtained. In most of the animals rises in blood pressure were seen during stimulation of the hypothalamus or other parts of the brain but always in association with muscular movements, often violent in character. Cat 19 furnished an excellent contrast between the effects of electric stimulation of the "vasomotor centers" in the floor of the fourth ventricle and the posterior part of the hypothalamus. Weak currents (the induction coil at 10 cm.) produced a moderate depressor effect on blood pressure from medullary stimulation. Stronger currents (induction coil at from 7 to 5 cm.) produced unequivocal rises in arterial pressure *without any muscular movements.* On the other hand, stimulation of the posterior hypothalamus with currents insufficient to produce muscular movements had virtually no effect on blood pressure. Even a current of 7 volts (from a McIntosh machine) which brought about muscular movements produced no response in blood pressure. In the latter part of this series of animals (cats 45 to 49) there were no significant changes in blood pressure in spite of muscular movements.

In all experiments with ether anesthesia it was noted that the degree of anesthesia had a profound effect on the blood pressure and on the muscular response to stimulation of the hypothalamus or other parts of the brain. As might be expected, a weaker stimulus produced a greater rise in blood pressure and more violent body movements in a cat under light anesthesia than did the same or a stronger stimulus in a cat under deep anesthesia. All possible transitions of response could be obtained simply by varying the depth of anesthesia. However, under

TABLE 4.—*Effect of Curarization on Results of Hypothalamic Stimulation in Cats of Group D; Approach to Hypothalamus Through the Mouth; Ether Anesthesia*

Cat	Degree of Anesthesia	Strength of Stimulus (Coil Distance), Cm.	Duration of Stimulus, Sec.	Body Movements	Blood Pressure: Before, Mm. of Mercury	Blood Pressure: During, Mm. of Mercury	Blood Pressure: After, Mm. of Mercury	Respiration	Anatomic Site of Stimulation	Comment
77	Mod.* deep	8.5	35	++	144	162	138	Slowed	Right side of midhypothalamus	Before curare
	Mod. deep	8.5	30	++	134	150	120	Slowed		12 min. after 5.6 mg. of curare per Kg.†
	.....	8.5	25	++	84	110	88	Hyperpnea		Pain? Artificial respiration begun 35 min. after curare
	Mod. deep	8.5	25	±		No effects		.....		40 min. after curare
	Light	7.5	28	±		No effects		.....		42 min. after curare
	Light	7.0	10	+++	80	104	76	Apnea		43 min. after curare
79	Light	8.5	18	++	124	136	124	Slowed	Midhypothalamus, medial	Before curare
	Light	8.0	20	+++	116	140	76	Apnea		Before curare
	Light	8.0	8	++++	110	136	64	Apnea		7 min. after 6.2 mg. of curare per Kg.‡
	Very light	8.5	10	+	90	96	84	Slowed		30 min. after curare
	Very light	8.0	13	++	84	94	84	Apnea		32 min. after curare
	Very light	8.0	10	+	76	80	72	Apnea		34 min. after curare
80	Light	8.0	22	++	146	164	146	Slowed	Anterior part of hypothalamus, bilateral, chiefly on right side, medial	Before curare
	Light	8.0	18	++	150	162	140	Apnea		11 min. after 6.9 mg. of curare per Kg.
	Very light	8.0	20	±		No effects		No effect		23 min. after curare (artificial respiration)
	Very light	7.5	15	+		No effects		Slowed		24 min. after curare
	Very light	7.0	24	+++ T‖	144	176	160	Hyperpnea		25 min. after curare (cat awake)
	None	7.5	15	+	134	146	130	Deeper		30 min. after curare
	Deep	7.0	10	0		No effects		Increased		32 min. after curare
	Light	7.0	20	+	124	136	136	Deeper		42 min. after curare (pupils dilated)
	Light	6.5	27	++ T	126	186	98	Deeper		44 min. after curare (pain ?)
	Deep	6.5	23	±	132	144	144	Deeper		47 min. after curare
	Very light	6.5	30	++	116	166	116	Apnea		69 min. after curare
	None	6.5	48	+++ T	90	174	122	Apnea		100 min. after curare (spontaneous respiration)
81	Light	8.0	12	+++	106	120	82	Hyperpnea	Posterior part of hypothalamus on right side	Before curare
	Deep	8.0	15	++	90	100	86	Hyperpnea		Before curare
	Light	8.0	20	+	90	97	74	Hyperpnea		15 min. after 7.7 mg. of curare per Kg.
	None	8.0	30	+	94	98-80	82	Slowed		30 min. after curare
	Light	7.0	15	+++ T	90	166-80	64	Apnea		33 min. after curare
	Light	7.0	15	+++ T	90	144-90	80	Hyperpnea		42 min. after curare
	Mod. deep	7.0	33	++	98	118	100	Hyperpnea		50 min. after curare
83	Light	9.0	26	+	142	158	136	Slowed	Anterior part of hypothalamus	Before curare
	Light	8.5	22	++	142	172	114	Apnea		Before curare
	Light	9.0	23	+	154	166	150	Apnea		5 min. after 19.6 mg. of curare per Kg.
	Light	8.5	26	±	160	172	160	Slowed		10 min. after curare
	Mod. deep	8.5	22	0	170	176	174	Slowed		13 min. after curare
	Mod. deep	8.5	8	0		No effects		.....		15 min. after curare
	Mod. deep	8.0	20	++	172	198-140	132	Apnea		16 min. after curare
	Light	8.5	25	±	168	188	152	Slowed		25 min. after curare
	Light	8.5	25	0	168	173	170	.....		30 min. after curare
	Light	8.0	32	±	166	194	186-166	Slowed		31 min. after curare
		Apnea for	20	0	128	146	124	.....		44 min. after curare
	None	8.0	27	±	68	76	76	.....		46 min. after curare
	Deep	Apnea for	55	0	102	152	102	Apnea		82 min. after curare
	Deep	7.5	18	0	106	116	104	Deeper		84 min. after curare
	Deep	7.0	35	0	105	132	100	Deeper		86 min. after curare

84	Light	8.0	30	++	48	60	50	Hyperpnea	Hypothalamus	Before curare
	Light	8.0	32	++	54	68	54	Hyperpnea		Before curare
	Light	8.0	33	+++	76	92-70	64	Hyperpnea		10 min. after 10 mg. of curare per Kg.
	Light	8.0	17	+	76	88	82	Slowed		15 min. after curare
	None	8.0	30	±	78	88	90	Deeper		20 min. after curare (artificial respiration)
	None	8.0	32	+	74	100	78	Deeper		30 min. after curare (artificial respiration)
	None	7.5	48	± T	58	140	132-176	Increased		33 min. after curare (artificial respiration)
	None	8.0	30	±		No effects		.....		37 min. after curare (artificial respiration)
	None	Asphyxia for	70	0	80	120	...	Asphyxia		47 min. after curare (artificial respiration)
85	Light	8.0	18	++	90	110	80	Apnea	Left side of	Before curare
	None	8.0	12	++	110	120	90	Apnea	midhypo-	8 min. after 12.5 mg. of curare per Kg.
	None	8.0	30	Very slight		No effects		Deeper	thalamus	20 min. after curare (artificial respiration)
	None	7.0	28	±		No effects		Hyperpnea		22 min. after curare (artificial respiration)
	None	Apnea for	38	0	60	70	62	Apnea		24 min. after curare (artificial respiration)
	None	6.5	25	0	72	80	72	.....		31 min. after curare (artificial respiration)
	None	6.0	30	0	76	106	100-80	Deeper		34 min. after curare (artificial respiration)
	None	4.0	20	+ T	62	82	70-58	Hyperpnea		45 min. after curare (artificial respiration)
	Deep	4.0	30	0	30	44	30	Hyperpnea		48 min. after curare (artificial respiration)
88	Light	8.0	20	++	122	138	122	Slowed	Middle lateral	Before curare
	Light	7.5	20	+++	120	150	84	Apnea	right side of	Before curare
	Light	8.0	18	+	102	110	96	Slowed	hypothalmus	5 min. after 5.4 mg. of curare per Kg.
	Light	8.0	12	±		No effects		Slowed		14 min. after curare
	Light	7.5	13	+	88	100	80	Apnea		16 min. after curare
	Light	7.5	15	+++	80	136	76	Hyperpnea		21 min. after curare (artificial respiration)
	Light	7.5	43	+++ T	80	138	96	Hyperpnea		28 min. after curare (artificial respiration)
	None	...	110	0	100	118	94	Asphyxia		30 min. after curare (slow spontaneous respiration)
	None	7.5	32	++ T	90	162	...	Apnea		33 min. after curare
88b	Light	8.5	22	++	110	138	106	Apnea	Subthalamus	Before curare
	Light	8.5	22	+	148	154	130	Slowed	and hypo-	10 min. after 6.5 mg. of curare per Kg.#
	Very light	8.5	15	±	142	142	128	Slowed	thalamus	17 min. after curare
	Very light	8.5	32	+	142	146-132	132	Apnea		25 min. after curare
	No ether	8.0	20	0		No effects		No effect		46 min. after curare (artificial respiration)
	No ether	8.0	35	+++ T	116	156	84-108	Apnea		50 min. after curare (artificial respiration)
	No ether	7.5	18	++ T	116	146	104-116	Hyperpnea		55 min. after curare (artificial respiration)
	Light	6.0	20	++++ T	82	190	96	Slowed	Roof of midbrain	85 min. after curare (artificial respiration)
	Light	6.0	18	++++ T	96	192	90	Slowed	Hypothalamus	90 min. after curare (artificial respiration)
90	Light	6.5	10	+++	106	150	100	Apnea	Midhypo-	Bipolar stimulation before curare
	Very light	7.5	10	++	140	176	112	Apnea	thalamus and	Bipolar stimulation before curare
	Mod. deep	7.5	15	Slight	146	156	116-142	Increased	thalamus	Bipolar stimulation before curare
	Light	7.5	30	Walking	138	152	128-138	Increased		10 min. after 8.5 mg. of curare per Kg.
	Light	7.0	30	Walking	126	142	120	Hyperpnea		19 min. after curare (artificial respiration)
	Light	7.0	28	±	76	88	82	.....		24 min. after curare
	No ether	6.5	40	0	84	104	96	Increased		34 min. after curare (pupils dilated)
	No ether	6.5	25	± T	84	100	98	Deeper		36 min. after curare; unipolar stimulation
	No ether	6.0	45	0	92	106	98	Slowed		41 min. after curare; bipolar stimulation
	No ether	6.0	26	± T	102	112	106	Slowed		44 min. after curare; unipolar stimulation
	No ether	5.5	30	±	84	98	92	Slowed		49 min. after curare; bipolar stimulation
	No ether	5.5	30	± T	88	104	92	Slowed		50 min. after curare; unipolar stimulation
	No ether	4.5	25	± T	86	90	90	Slowed		54 min. after curare; bipolar stimulation
	No ether	4.5	25	+	90	104	84	Deeper		55 min. after curare; unipolar stimulation

* Mod. = moderately.
† Time elapsed from initial dose of 20 mg. of curare at 2:48 p. m. Another dose of 15 mg. was injected at 3:07 p. m., and 5 mg. more at 4:08 p.m.
‡ Time elapsed from initial dose of 20.5 mg. of curare at 2:10 p. m. Another dose of 10 mg. was injected at 2:29 p.m.
‖ T indicates tonic movements.
Time elapsed from initial dose of 20 mg. of curare at 2 p. m. Another dose of 20 mg. was given at 2:35 p. m.

no circumstances were significant pressor responses found without muscular movements, even under light anesthesia.

C. Ether Anesthesia; Karplus and Kreidl Approach (table 3).—This series of cats included those between numbers 50 and 76, also cat 45. By the method of Karplus and Kreidl, the hypothalamus was exposed and, under visual control, was stimulated in various areas. In general the results were similar to those previously described: absence of any effect on the blood pressure when muscular movements were not elicited, and rises in blood pressure more or less proportional to the degree of muscular movement and often followed by considerable drops in blood pressure during the stage of relaxation. Abolition of the effects of both movements and blood pressure were noted on deepening the degree of ether anesthesia. There seemed to be no significant difference between the effects of stimulation of the anterior, middle and posterior portions of the hypothalamus, if allowance is made for the degree of muscular activity and the proximity of the area stimulated to the ipsilateral cerebral peduncle.

In cats 53, 64, 65, 66 and 67 the left peduncle was stimulated with varying strengths of current comparable to stimuli applied to the hypothalamus. The results of such stimuli were invariably the same type of muscular movements and rises in blood pressure corresponding to the degree of such movements that were obtained from the hypothalamus. Also, when no movements were obtained from the peduncle with weaker stimuli, no significant pressor responses were recorded. A given strength of stimulus when applied to the peduncle usually produced more marked effects than when applied to the hypothalamus. This is well shown in cats 53, 64 and 65.

In cats 45, 51 and 52 the responses on the part of the blood pressure were, in general, decreases rather than rises, even though muscular movements occurred with each stimulation. It is interesting to note that the fall in blood pressure when elicited in a cat could be obtained from stimulation of various areas of the hypothalamus and other parts of the brain.

Cat 70 was an extremely interesting exception in that a sustained elevation of arterial pressure was obtained even with weak stimuli. Also there was no fall in blood pressure below the control level on the cessation of the stimulus. However, the muscular movements were tonic, instead of the usual clonic type. It should be emphasized that the anterior part of the hypothalamus was the area stimulated in this cat.

D. Experiments with Curare (table 4).—In cats 77 to 90, curare was employed in an attempt to control or eliminate the factor of muscular activity in relation to pressor responses on excitation of the hypothalamus. While there was considerable variation in the effect obtained

by curare because of inadequate dosage in some of the experiments and irregular drug activity in others, there is no question as to the parallelism of muscular movements and changes in blood pressure. In cats 80, 83, 85, 88, 88b and 90 fairly good curarization was followed by absence of muscular activity and little or no rise in blood pressure on strong stimulation of the hypothalamus. In cats 83, 84, 85 and 88 the rises in blood pressure, which were apparently out of proportion to the degree of muscular activity, could be to a considerable extent reproduced by brief interruption of artificial respiration comparable in degree to what actually occurred during the stimulation. In other words, we were dealing with an asphyxial rise in blood pressure in animals with a hypersensitive medullary vasomotor mechanism. In cat 84, however, rises in blood pressure amounting to 82 mm. were obtained in the presence of only slight movements and in the absence of any appreciable disturbance of respiration. It is to be noted that when the current used was strong enough to break through the curarized nerve endings, the convulsive activity was usually of the tonic rather than of the clonic form seen in noncurarized animals.

In cat 88b, for purposes of control, the superior surface of the midbrain (roof of the third ventricle) was stimulated with a current sufficiently strong to break through the effect of curare and produce tonic convulsions. A rise in blood pressure of 108 mm. occurred. Five minutes later, the same stimulus applied to the hypothalamus resulted in the same muscular response and in a rise in blood pressure of 96 mm. Deepening of the anesthesia wiped out the effects of stimulation from both areas.

In cat 90 unipolar and bipolar stimulation were compared after curarization of the animal. The effects were essentially the same, even with very strong stimuli.

ANATOMIC RESULTS

For the most part, serial sections were made of the hypothalamus and were carefully studied to identify the nuclear areas through which the electrode had passed. In the later experiments the gross description of the site of the electrode was sufficient to identify the nuclear area stimulated.

The areas stimulated have been given in detail in the correlation tables. In general it may be stated that no physiologic results obtained in our experiments could be attributed to stimulation of a definite nuclear mass. Effects on the respiration, pupils and somatic musculature were obtained from any region of the hypothalamus. Conversely, negative results in regard to blood pressure were obtained from all parts of the hypothalamus when weak currents were used and movements were not produced.

COMMENT

A. Physiologic Data.—The original plan of this investigation was to determine in a simple direct manner whether or not there existed a vasomotor "center" in the hypothalamus. From the work of Karplus and Kreidl, apparently confirmed later by the more detailed studies of Beatty, Brow and Long, as well as by those of Wang and Richter, it seemed possible to obtain uncomplicated vasomotor responses from certain regions of the hypothalamus. The few published tracings of the blood pressure curves lead one, however, to considerable skepticism concerning the results. This we have already alluded to in the introductory part of the study. Furthermore, a critical glance at text figure 3 of the contribution by Beatty, Brow and Long [28] indicates that the rise in blood pressure amounted to no more than from 26 to 34 mm. of mercury with as strong a stimulus as a coil distance of 8 cm. on a 3 volt circuit. Wang and Richter gave no tracings, but they stated in a personal communication that the rises in blood pressure in their experiments were not constant, and that frequently drops in blood pressure were obtained. Respiratory phenomena were not recorded, and movements were not recalled by them.

However, in our first experiments we observed numerous complications which rendered the interpretation of pressor phenomena extremely difficult. As has been pointed out in the section concerned with results, it is virtually impossible to stimulate any portion of the hypothalamus with an electric current strong enough to produce vasomotor effects without at the same time eliciting striking somatic muscular movements and respiratory changes. The nature of the movements varies with the strength of the stimulus, and the latter, in turn, with the depth of anesthesia. There is a similar correlation between the strength of the stimulus, the depth of anesthesia and the respiratory abnormalities.

As to the movements, with very weak stimulation there would usually be either a single slight tonic twitch of the head and neck or a few clonic twitches spreading at times to the forelimbs. With stronger stimulation the twitching would spread to the thoracic and abdominal musculature and to the lower extremities. Still stronger stimuli produced powerful tonic convulsions with opisthotonos. The clonic or tonic movements of the cervical muscles were often a serious problem in the recording of blood pressure from the common carotid artery. We therefore sectioned the muscles of the neck and shoulder on the side from which the blood pressure was recorded in order to free the artery. The muscular contractions were observed under both dial and ether anesthesia. With the latter anesthetic it was possible to diminish or entirely to abolish the movements by deepening the narcosis. In

28. Beattie, Brow and Long,[18a] p. 257.

this case, however, a given stimulus would no longer produce any effect on blood pressure, but as the strength of the current was increased by decreasing the coil distance, muscular activity would again appear, and with it changes in blood pressure. While absolute correlation did not exist, there is little doubt that in general the greater rises in blood pressure occurred with the more violent movements and particularly with the tonic convulsions. This relationship is further strengthened by the fact that in most instances a marked rise in blood pressure during the height of the convulsions would be followed by an equivalent or even greater fall in blood pressure on cessation of the stimulus and sudden relaxation of the musculature. The return to the control level would then take place fairly rapidly except in those instances in which narcosis was deepened by the hyperpnea following the convulsions. In all but the minimal movements bilateral and more or less symmetrical activity was observed, even when the electrode was inserted in one lateral hypothalamic area.

With very light or almost no anesthesia, the type of muscular response was somewhat different. in that there would be slow lashing of the tail, straining at the tie straps or walking movements of the extremities, licking movements of the tongue and rolling of the eyes–all of which suggested a response to a painful stimulus. Here again there was no disproportionate rise in blood pressure that one could attribute to irritation of a vasomotor center in an animal scarcely anesthetized.

The nonspecific nature of the muscular movements just described was well demonstrated by the complete similarity of movements resulting from adequate stimulation of other parts of the brain, such as the motor cortex, roof of the third ventricle and the thalamus. Here, also, there was not only a correlation between the degree of movements and the height of rise in blood pressure, but the actual type of blood pressure curve was often indistinguishable from that obtained during the hypothalamic irritation. Furthermore, the effects on both blood pressure and movements were influenced in the same manner by depth of anesthesia whether the hypothalamus or other areas of the brain were stimulated. It usually required a stronger current to produce a given effect from regions of the brain other than the hypothalamus.

The most interesting control experiments in regard to this question of muscular movements were those involving successive direct stimulation of one cerebral peduncle and the hypothalamus in the same animal, with the same strengths of current and the same degree of anesthesia, so that conditions were as comparable as possible. In such animals, a stimulus which was too weak to produce any effect whatever from any region of the hypothalamus might give rise to slight muscular activity and to a corresponding rise in blood pressure when applied to the intact

cerebral peduncle. On increasing the strength of stimulus to the hypothalamus there would occur, of course, movements and associated rises in blood pressure. However, the effects of these same increasing stimuli when directed to the peduncle would be much more marked. When the stimulus was not strong enough to produce violent convulsions, the motor effects from the peduncle were contralateral to the site stimulated. From the hypothalamus they were bilateral.

The last link in the series of controls on the pressor effects of muscular movements necessitated the use of curare, particularly since in almost all the experiments no appreciable effect could be detected in the blood pressure curve following the use of stimuli too weak to produce muscular contractions. It is interesting that Karplus and Kreidl [10] used curare in some of their experiments but made no mention of the reason for its use. Even in the curarized animals a rise in blood pressure was not constantly obtained on stimulation of the hypothalamus and was not related to pupillary dilatation or other recognized results of hypothalamic irritation. Owing to difficulty in obtaining the drug, only ten of our cats were curarized and in good enough condition to yield successful experiments, but the results were so clearcut that we are confident of their reproducibility in a larger series.

With a given strength of stimulus producing a given rise in blood pressure coincident with a certain degree of muscular activity in a control period, the effect of curarization was to diminish or abolish these responses not only to the given stimulus but to much stronger stimuli. The actual degree of electric excitation tolerated by the animal naturally varied with the depth of anesthesia. In some instances, with practically no anesthesia at the time of stimulation, a fairly strong current would produce not the usual clonic or tonic movements, but feeble walking movements, unsheathing of the claws and some lashing of the tail. If the stimulus was so strong as to break through the curare paralysis, a marked rise in blood pressure with a plateau curve might occur, associated with varying degrees of tonic contraction, at times only a single twitch. In case of the more violent movements, just as striking a rise in blood pressure could be obtained from stimulation of some part of the brain other than the hypothalamus. Deepening of the anesthesia would diminish the effects of stimulation of any region in a comparable manner. In cats 84 and 85, the rises in blood pressure after curarization were out of all proportion to the slight movements, and, had they followed weak stimuli, would certainly be significant.

"The question may well arise as to why other investigators doing experimental work in the region of the tuber cinereum have not noted convulsions in their animals" (Morgan and Johnson [17b]). The same question has repeatedly occurred to us, and we are as little able to answer it as the authors quoted. Morgan and Johnson observed clonic

and tonic convulsions in dogs after 0.1 cc. of a 0.3 per cent solution of mercuric chloride had been injected into the hypothalamus in the region of the tuber cinereum. The blood pressure was recorded in two of these animals when they were in a state of coma and status epilepticus. In the single tracing reproduced,[17e] the blood pressure rose from the control level of 140 mm. of mercury to 180 mm. about twenty seconds before the onset of the muscle spasms and then to 200 mm. during the height of the convulsion, falling back to 140 mm. within a few seconds after the cessation of movements. The heart rate increased from 184 to 231 per minute. The authors presented no evidence of a rise in blood pressure in the absence of convulsions with this method of chronic irritation of the hypothalamus. Morgan and Johnson went so far as to postulate an epileptogenous zone in the tuber cinereum from which there occurred a general discharge of autonomic impulses. It is interesting to contrast these experimental results with the observations recorded by Penfield [20] in a case of ball valve tumor in the third ventricle, in which there apparently occurred an autonomic discharge with marked changes in blood pressure but without convulsions and rarely with loss of consciousness. Penfield labeled this syndrome "diencephalic autonomic epilepsy" and emphasized that the pressure of the tumor was above and anterior to the hypothalamus, in other words, over the thalamus, which he considered the highest representation of the autonomic nervous system.

It is obvious from the preceding considerations that the interpretation of pressor responses from stimulation of the hypothalamus is impossible without extremely critical control of the by-products of irritation of that portion of the brain. Considerably more work must be done before the conception is established of a zone in the hypothalamus which, when stimulated, gives rise to muscular movements. The structures that form the efferent pathways over which the stimulus travels to evoke muscular movements are not easy to determine, but one would guess that the proximity of the medial portion of the cerebral peduncle to the posterior part of the hypothalamus would facilitate a spread of current. As we have shown in our results, it requires a certain strength of current to produce slight movements limited to the head and neck, but a stronger current to cause more widespread motor activity and changes in blood pressure, the latter two being more or less parallel in degree. Anatomically, this fits in with feasible spread, for the more proximal (medial) fibers of the peduncle are destined to innervate the upper portion of the body and hence would be stimulated by weaker currents. A more marked response obtained from directly stimulating the peduncle with the same strength of current as applied to the hypothalamus is also suggestive of spread of current.

In fact, there is considerable evidence that somatomotor and visceromotor suprasegmental fibers use pathways in close proximity to each other. Langworthy and Richter [29] demonstrated action currents indicative of stimulation of sweat glands when they irritated the rubrospinal, corticospinal and vestibulospinal tracts, the cerebral cortex, the cerebral peduncles or the hypothalamus. They believed that excitation or inhibition of sweat glands is effected through the same paths through which excitation or inhibition of the somatic common pathway occurs. Furthermore, Friedberg,[30] stimulated by Spiegel's views on the cortical representation of the vegetative system and the close association of vegetative and somatic fibers in the central nervous system, extirpated the motor cortex in cats and stimulated the internal capsule at varying intervals thereafter. He found that as long as the pyramidal fibers were still intact electric stimulation gave rise to muscular movements, pupillary dilatation and rises in blood pressure. However, after degeneration of the pyramidal tract, no rise in blood pressure resulted from stimulation of the cerebral cortex or subcortex, just as no movements occurred. In other words, there was no evidence of dissociation of sympathetic and somatic fibers, but the results suggested that the efferent pathways of both are in juxtaposition or possibly use the same fibers. It would seem possible that results obtained from stimulation of the hypothalamus may be the effect merely of irritation of the somatic pathway rather than of a center. It should be pointed out that Karplus and Kreidl must have gone through the cerebral peduncle in order to stimulate the subthalamic body.

The association of an elevated arterial pressure with experimental convulsions of whatever origin (and hence the necessity of completely eliminating muscular activity during stimulation of alleged vasomotor centers) has been clearly demonstrated in the studies of Coombs and Pike,[31] Coombs [32] and Notkin, Coombs and Pike.[33a] In their investigation of convulsions caused by monobromated camphor and absinth under carefully controlled conditions, they observed marked rises in blood pressure during the height of the seizure at a time when both muscular activity and asphyxia were in full play. After the administra-

29. Langworthy, O. R., and Richter, C. P.: The Influence of Efferent Cerebral Pathways Upon the Sympathetic Nervous System, Brain **53**:178, 1930.

30. Friedberg, C. K.: Zur Frage der Identität der corticalen somatischen und vegetativen Zentren nach Reizversuch an der degenerierten inneren Kapsel, Ztschr. f. d. ges. Neurol. u. Psychiat. **134**:50, 1931.

31. Coombs, H. C., and Pike, F. H.: Am. J. Physiol. **97**:92, 1931.

32. Coombs, H. C.: The Effects of Repeated Electrical Stimulation of the Cortical Motor Area in the Cat, Am. J. Physiol. **100**:64, 1932.

33. (*a*) Notkin, J.; Coombs, H. C., and Pike, F. H.: Am. J. Psychiat. **11**: 679, 1932; (*b*) ibid., p. 698.

tion of curare, the injection of the chemical convulsant led to a marked fall in blood pressure, indicating the predominance of skeletal muscular effect over central vasomotor effect. Notkin, Coombs and Pike stated: "The rise in blood pressure during a convulsion is due to the activity of the skeletal musculature and not to any direct action upon the vasoconstrictor mechanism." [33b]

The respiratory effects of hypothalamic stimulation have puzzled investigators ever since the original work of Karplus and Kreidl, and of Aschner.[9a] These authors described a type of dyspnea which was strongly suggestive of the respiratory effects of pain; in fact, Aschner stated that the animals actually cried out even under deep anesthesia. This was sufficient evidence to him that the hypothalamus was definitely sensitive to painful stimuli, and he assumed stimulation of sensory pathways from the trigeminal or vagus nerves. Simply puncturing the floor of the third ventricle with a needle, in a deeply narcotized animal, resulted in an outcry (*Schreien*), with dyspnea, marked bradycardia or even cardiac standstill. The problem of pain sensitiveness of the hypothalamus was further investigated by Karplus,[14] who was able to demonstrate the effect in monkeys as well as in cats. The outcry occurred even after decerebration, thus ruling out conscious pain. The hypophysis itself was entirely insensitive. Electric stimulation sufficient for the hypothalamus would produce no effect from the thalamus. Karplus wondered about a pseudo-affective reflex. He stated that in 170 patients operated on under local anesthesia by O. Hirsch, no pain was observed from irritation of the floor of the third ventricle. However, traction on the hypophyseal stalk caused very severe pain which was referred only to the center of the head. Karplus was careful to emphasize the difference between the human and the animal cortex and the dangers of reasoning by analogy in regard to pain.

Ranson,[34] using the Clarke stereotaxic machine, made many electric exploratory stimuli of the hypothalamus, accurately checking the site stimulated by anatomic studies. The characteristic response which he observed was an increased rate and depth of respiration with weak currents in the unanesthetized animal suspended in a hammock. These respiratory changes were not recorded graphically, nor were simultaneous readings of the blood pressure obtained. There were occasionally turning movements of the head or progression movements of the legs, but no convulsions occurred with weak currents. The sites from which respiratory effects were obtained extended over much of the hypothalamus, but were mainly in the lateral and posterior portions. There

34. Ranson, S. Walter: Experiments on the Hypothalamus, Arch. Neurol. & Psychiat. **29**:1179 (June) 1933.

were no localized areas, but many points in the several hypothalamic nuclear configurations, when stimulated, would produce respiratory changes.

Typical panting or polypnea has been described by Keller and Hare [35] in cats with the whole of the hypothalamus severed from the midbrain and lower segments of the neuraxis. The phenomenon was interpreted as a release of the mechanism controlling heat loss, located in parts unknown, from coordinated control by the mechanism of heat production which is situated in the hypothalamus. It seems to us that these observations may explain some of the respiratory effects of direct electric stimulation of certain portions of the hypothalamus, since it has been shown that the heat center may be stimulated by electric and chemical, as well as by thermal, changes.

In the vast majority of our own experiments the respiratory phenomena from hypothalamic stimulation were relatively simple and predictable. Under light anesthesia and with mild electric stimuli, the respiration would usually be slowed for a few phases and then perhaps increased in rate and depth. Usually the response of respiration was slightly more sensitive to a given stimulus than the response of the musculature or of the blood pressure. Stronger irritation brought about tetanic apnea, followed at the cessation of current by increased amplitude and rate, so that deeper narcosis might result from the hyperventilation subsequent to convulsions. In a few animals (cats 21, 66, 67a and 76) definite stimulation of respiration occurred simultaneously with muscular movements. This was also the case in two dogs studied with the same method of approach to the hypothalamus and stimulation through the buccal region, but took place only with weaker stimuli and under light anesthesia. With the longer, if not too strong, stimuli, there was a preliminary period of apnea followed by resumption of slowed respiration before the stimulation ended. In cat 34, with 0.2 cc. of 1.0 per cent mercuric chloride injected into the hypothalamus, a peculiar periodic respiration developed, consisting essentially of one inspiration followed by five or six small expiratory movements. There was considerable prolongation of expiration. This phenomenon lasted only a few minutes after the injection, but recurred on introduction of the electrode into the hypothalamus. It disappeared again after a violent convulsion produced by electric stimulation. From the few experiments involving stimulation of the third ventricle (cats 8 [dial] and 52), it seems that much more pronounced respiratory effects could be produced from this region than from other areas. Slowing of respiration, irregular breathing and tachypnea were the chief changes.

35. Keller, A. D., and Hare, W. K.: Proc. Soc. Exper. Biol. & Med. **29**: 1069, 1932.

In some of the experiments with curare and artificial positive pressure respiration, it was noted that stimulation of the hypothalamus produced a definite increase in the amplitude of respiration, as though bronchiolar dilatation had occurred. This was particularly well seen in cats 85, 88 and 90. Also, in the curarized animals in which rises in blood pressure occurred with strong stimuli in the absence of muscular movements, it could be shown that the vasomotor center responded strikingly to temporary apnea. This reaction suggests that elevation of blood pressure occurring during muscular movements associated with apnea is partly the result of asphyxial stimulation of the medullary vasomotor center. The same conclusion was reached by Coombs and Pike [31] in their studies on chemical convulsants.

In cat 84, after curarization, a striking rise in blood pressure followed moderate stimulation with practically no associated muscular movement and no respiratory disturbance. While this reaction would seem to support the view of the presence of a vasomotor center in the hypothalamus, it does not rule out a usually sensitive medullary vasomotor center. Furthermore, Coombs [32] observed a similar disproportionate hypertension on stimulating the motor cortex in curarized cats, but offered no explanation for her results.

In regard to the outcry (*Schreien*) described by Karplus and Kreidl and by Aschner as resulting from stimulation, particularly of the floor of the third ventricle, we did not observe exactly that type of response, but in most of our animals either the upper end of the pharynx was well packed off with cotton or tracheal cannulation had been carried out. We did observe loud, harsh, irregular gasps resembling the respiratory stimulation from swabbing aside the periosteum of the hard palate in approaching the hypothalamus by the buccal method. If Krause's [36] conception is correct, that the secondary sensory pathways from the ninth and tenth cranial nerves run into the hypothalamus, the gasping may be thus explained. It would also seem reasonable that the sudden outcry of an animal under deep anesthesia is not a manifestation of pain, as has been assumed by Aschner, but is more likely due to sudden expulsion of air through upper respiratory passages rendered narrow by tonic contraction.

B. Anatomic Data.—The hypothalamus constitutes one of the major divisions of the diencephalon, containing centers mainly subserving the functions of olfactovisceral correlation. The nonolfactory portions of the hypothalamus consist of the optic chiasm and the supra-optic commissures of Gudden and Meynert. The olfactory component of the hypothalamus need not detain us long. The mamillary body receives fibers from the olfactory cortex by way of the fornix and direct

36. Krause, F.: Ztschr. f. klin. Med. **121**:563, 1932.

olfactory fibers from the anterior perforated space. The mamillary body sends fibers to the thalamus by way of the bundle of Vicq d'Azyr. The afferent fibers from the anterior portion of the hypothalamus to the mamillary body and from the latter to tegmental structures are still undetermined.

The structure of the central gray matter surrounding the ancient primitive neural tube in the region of the third ventricle has received little attention until lately, when its functional significance assumed importance. In 1914, Malone [37] studied the hypothalamus of cats, monkeys and man. He was able to homologize certain discrete nuclear collections composed of characteristically formed cells suggestive of a specific and isolated functional significance. Seven separate nuclei were defined. The ganglion mediale corporis mamillaris, the nucleus intercalatus corporis mamillaris and the nucleus tuberis lateralis constituted the mamillary body itself.

The nucleus tuberomamillaris, formerly termed infundibulomamillaris, is composed of fairly large cells in which the Nissl bodies are diffusely scattered throughout the cytoplasm. These cells extend from the mamillary body and radiate around the columns of the fornix, following it forward into the region of the tuber cinereum. The cells are not arranged in a compact nucleus but lie interspersed in the substantia grisea ventriculi tertii.

The nucleus paraventricularis hypothalami is composed of cells similar in size to the former group. It extends along the ventricular wall in both anterior (pars optica) and posterior (pars mamillaris) portions of the hypothalamus. The substantia grisea ventriculi tertii consists of small, relatively undifferentiated cells, most numerous and closely packed in the pars optica.

The basal optic ganglion, or supra-optic nucleus, lies partly in the tuber cinereum and anterior perforated space, overlying the oral-lateral surface of the optic tract. It consists of two parallel columns of cells. They are large polygonal cells with coarse processes and Nissl substance in the periphery of the cell body.

The nucleus tuberis lateralis comprises several small discrete groups of small cells in the lateral tuber, differentiated from the small cells of the substantia grisea. They have little Nissl substance, and in man they contain cytoplasmic pigment.

Greving [38] has recently studied the hypothalamus and its connections and added new data. He described the nucleus supra-opticus in greater

37. Malone, E. F.: The Nuclei Tuberis Laterales and the So-Called Ganglion Opticum Basale, Johns Hopkins Hosp. Rep., Monog. 11, 1914.

38. Greving, R.: Diencephalon, in von Möllendorf: Handbuch der mikroscopischen Anatomie des Menschen, Berlin, Julius Springer, 1927, vol. 10.

detail and recognized the characteristic cells of the nuclei tuberis, nucleus paraventricularis and substantia grisea. The nucleus pallido-infundibularis and interfornicatus were also outlined. He found that the supra-optic nucleus sends fibers to the posterior lobe of the pituitary body and another dorsally directed bundle, the ending of which is not known. The nucleus paraventricularis sends a fiber bundle ventrally toward the nucleus supra-opticus, but its ending is uncertain. A pathway to the nuclei tuberis comes from the frontal lobe through the ansa peduncularis. The substantia grisea centralis and substantia reticularis send fibers along the floor of the third ventricle toward the aqueductal region. Greving suggested the following hypothetic localization of function in the hypothalamus: nucleus supra-opticus, water regulation (thirst); nuclei tuberis, temperature regulation; substantia grisea, genital and fat regulation; nucleus paraventricularis, carbohydrate metabolism (hunger), and subthalamic body, vasomotility, sweat secretion and bladder control. It is interesting to note the numerous hypothetic cortico-hypothalamic and thalamohypothalamic pathways that Greving postulated. However, descending fibers apparently go only in a dorsal pathway in the median longitudinal fasciculus and in a smaller ventral fiber system in the mamillary peduncle.

Beattie, Brow and Long [18a] deduced from Greving's work that the hypothalamus could be divided into two parts, the supra-optic infundibular complex and the tuber-paraventricular complex. They attempted to trace the fibers from the latter nuclear group down the neuraxis. Their operative mortality from lesions in the posterior part of the hypothalamus was high, only 7 of 16 animals used surviving, and only 2 living sufficiently long for the Marchi method to be employed. This method is unreliable for anatomic studies, especially when small tracts composed of fibers are to be followed. The Marchi preparations were interpreted as showing that some fibers from the posterior part of the hypothalamus passed forward into the median forebrain bundle after decussating in the supra-optic commissure. Ventral to the lesion, fibers crossed the midline in the decussation of Forel and passed down on the ventral and lateral aspects of the cerebral aqueduct. Some fibers ended in the mesencephalic tegmentum in the reticular formation. Others could be followed down to the pons, medulla and spinal cord as far as the third and fourth lumbar segments. Thus a single neuron is postulated running in the reticular structures from the hypothalamus to successive levels of the neuraxis as low as the lumbar cord. Scrutiny of the illustrations of the Marchi granules which indicated the degenerated nerve fibers leaves much to be desired, for the granules are differentiated with difficulty from the artefacts so frequently obtained in this complicated method, which often gives confusing results even in expert hands.

Gurdjian [39] was unable to follow the mamillotegmental tracts further than the level of the third nerve nucleus in the rat. This author found a complicated system of nuclei and separated the supra-optic complexes from the hypothalamic area for conventional reasons and not on morphologic grounds. Connections were found with the olfactory cortex by the median forebrain bundle, cortex, striatum and thalamus.

The mamillary nuclei, according to Huber and Crosby,[40] are connected with the hypothalamic nuclei. The mamillary body is apparently connected with the tegmentum by the mamillary peduncle. However, some anatomists believe that ascending fibers reach the hypothalamus by way of this peduncle from the median lemniscus, probably gustatory fibers, according to Cajal. The mamillothalamic and mamillotegmental tracts arise as bifurcations of single axons from the mamillary cells. The latter tract terminates in the dorsal tegmental nucleus and the interpeduncular nucleus. Thence, by way of the dorsal longitudinal bundle of Schütz, fibers are carried to the medullary visceral nuclei. Older anatomists thus recognized several neurons concerned in the influences of the posterior part of the hypothalamus on lower centers. Huber and Crosby, on the basis of their summary, indicated such a neural chain.

Krause [36] studied the secondary degeneration by the Marchi method after producing a "sugar puncture" in the fourth ventricle. He found Marchi granules ascending the tractus solitarius and median lemniscus to end in the contralateral mamillary body, subthalamic region, tuber cinereum and central gray of the aqueduct. Again, this would be good evidence for a single neuron reaching from the medulla to the hypothalamus if the Marchi granules were as definite and clear as could be desired. There is great difficulty in interpreting this method and, according to Poljak,[41] it is the posterior median region of the brain stem which shows black granules even though lesions have been made in far distant, unconnected areas.

Hiller and Grinker,[42] in some work concerned with the regulation of carbohydrate metabolism, studied the problem by another and more trustworthy method, that of axonal reaction or primary irritation of a cell after damage to its fiber. It was shown that, contrary to the opinion of Brugsch, Dresel and Lewy,[43] the vagus and cervical sympathetic

39. Gurdjian, E. S.: The Diencephalon of the Albino Rat, J. Comp. Neurol. **43**:1, 1927.

40. Huber, C. G., and Crosby, E. C.: Somatic and Visceral Connections of the Diencephalon, Arch. Neurol. & Psychiat. **22**:187 (Aug.) 1929.

41. Poljak, S.: Personal communication to the authors.

42. Hiller, F., and Grinker, R. R.: The Nervous Regulation of Sugar Metabolism, Arch. Neurol. & Psychiat. **22**:919 (Nov.) 1929.

43. Brugsch, I.; Dresel, K., and Lewy, F. H.: Zur Stoffwechselneurologie der Medulla Oblongata II, Ztschr. f. d. ges. exper. Med. **25**:262, 1921.

nerves do not contain fibers arising directly from areas higher than the medulla. But, for our purposes, experiments are more important when a hemisection of the medulla was made above the vagus nucleus and when, in other animals, complete degeneration of the vagal nuclei was effected. No change was found in the hypothalamic nuclei. This negative effect means simply that the hypothalamic influences on medullary centers are not by way of a single neuron, but by several intercalated neurons.

Karplus and Kreidl originally believed that their superior sympathetic center lay in the subthalamic body, although Beattie and others considered it to be located in the posterior portions of the hypothalamus. Morgan [44] studied the connections of the subthalamic body of Luys. Its efferent fibers end medially to the substantia nigra in scattered cells through the region dorsal to the mamillary body and red nucleus. They could be followed no further.

GENERAL COMMENT

The question of the localization of a regulatory vasomotor center in one or other of the nuclei of the hypothalamus or subthalamus was a problem which we had originally hoped to solve by first confirming that vasomotor effects could be obtained from the hypothalamus and then attempting to map out as accurately as possible by physiologic and anatomic studies just what nuclear structures were involved in this response. In our series of about ninety cats we succeeded in stimulating or irritating every possible portion of this subthalamic-hypothalamic area. The complexity of the reactions to hypothalamic irritations was such that it became evident that it made little difference in general what part of the hypothalamus was being stimulated. In many of the experiments the records show no significant variation between the results of stimulation of the anterior or posterior portion of the hypothalamus. The proximity of the latter to the cerebral peduncle is something which other authors have not considered. Beattie, Brow and Long stated unequivocally that the mechanism of the posterior hypothalamic area controls the thoracicolumbar outflow of the autonomic system and the secretion of epinephrine.

Beattie,[10] further, accepted Cushing's view that the anterior portion of the hypothalamus is the seat of a parasympathetic center. However, Beattie stated: "There is no direct evidence of the functional activity of the hypothalamus in the intact animal." Cushing's recent experiments on human beings when pituitary, pilocarpine or atropine sulphate

44. Morgan, L. O.: Symptoms and Fiber Degeneration Following Experimental Lesions in the Subthalamic Nucleus of Luys in the Dog, J. Comp. Neurol. **44**:379, 1927.

was injected into a lateral ventricle have opened a new vista in the entire problem of the possible control of autonomic activities by nuclei surrounding the third ventricle. However, even Cushing's work must be interpreted as evidence of higher parasympathetic and not sympathetic (in the strict sense) activity. In spite of obtaining striking parasympathetic phenomena, Cushing recorded two significant exceptions, namely, absence of pupillary constriction and lack of a significant effect on blood pressure.

It should be emphasized at this point that our experiments apparently contradict the conclusions of Beattie, Brow and Long in regard to a vasomotor center in the posterior part of the hypothalamus and, on the other hand, indicate the necessity for carefully controlled experiments on human beings along the lines initiated by Cushing. The attempt by Lawrence and Dial [27b] to repeat Cushing's experiments on unanesthetized dogs led to rather inconclusive results and, as the authors stated, reveals "marked differences in the reactions of man and dog to the effect of pituitrin and pilocarpine when introduced into the ventricle." The possible criticism that most of the earlier work on the vasomotor centers in the hypothalamus was done under dial anesthesia while most of our work was done under ether anesthesia would seem to be invalidated by the generally accepted view that the barbiturates narcotize the diencephalon while light ether anesthesia affects largely the cerebral cortex. It has taken much work on our part to demonstrate to our satisfaction that the problem of a superior vasomotor center in the hypothalamus is not as simple as it seemed at first. Furthermore, we are not certain that the available evidence for the existence of pupillary and respiratory centers in the hypothalamus is any better than the proof of a vasomotor center. The work of Beattie, Duel and Ballance,[45] indicating a very circumscribed pupillary center, may be contrasted with the recent work of Ranson.[34]

The uncertain state of the data obtained from animal experimentation, in which reasonably good control is possible, makes it easy to predict the value of the present clinical deductions as to the functions of the hypothalamus, particularly in regard to the regulation of blood pressure. Much more than the available clinical evidence is necessary to prove the existence of such a center. Careful clinical studies on patients with circumscribed lesions in the hypothalamus, supplemented by rigid morphologic control, will probably be the means of settling these important problems. At the present time it may be accepted as proved that injury to the supra-optic portion of the hypothalamus in man is

45. Beattie, J.; Duel, A. B., and Ballance, C.: The Effects of Stimulation of the Hypothalamic Pupillo-Dilator Center After Successful Anastomoses Between the Cervical Sympathetic and Certain Motor Nerves, J. Anat. **66**:283, 1932.

associated with polyuria or glycosuria, while lesions of the tuber cinereum are associated with obesity. The regulation of a great many other vegetative activities has been popularly referred to the hypothalamus, but this is still largely theory without sure foundation in fact.

SUMMARY AND CONCLUSIONS

1. Significant rises in arterial blood pressure uncomplicated by muscular activity or respiratory disturbances have not been obtained in this series of experiments on cats with direct electric stimulation of the hypothalamus. The site of stimulation was carefully controlled by histologic studies, and every possible subthalamic and hypothalamic area was found to have been stimulated.

2. When pressor effects were obtained, they could in general be correlated directly with the degree of muscular activity, the latter in turn being dependent for a given strength of stimulus on the depth of anesthesia.

3. The elimination of muscular movements by curarization of the animal was associated with a decreased pressor effect.

4. Significant hypertension occurred in curarized animals in which sufficiently strong stimuli were used to break through the effect of curare and cause tonic convulsions.

5. Tonic convulsions elicited from stimulation of the hypothalamus in a curarized animal caused no greater rise in blood pressure than similar movements obtained from irritation of other parts of the brain.

6. In animals under curare medication, in which the medullary vasomotor center is highly susceptible to the effects of apnea, electric stimulation of the hypothalamus may lead to considerable elevation of blood pressure in the absence of movements.

7. The muscular movements, chiefly clonic convulsions, secondary to hypothalamic stimulation were obtained with weaker strengths of current from the posterior part of the hypothalamus and the cerebral peduncles than from the anterior portion, and are interpreted as a result of a spread of current to the somatic motor fibers.

8. Respiratory phenomena from hypothalamic stimulation in most instances consisted of apnea during convulsions, but in a few non-curarized and curarized animals increased depth and rate of respiration were observed even in the absence of muscular activity.

9. The present series of experiments on a large number of animals lends no support to the view that there is a superior vasomotor center in the hypothalamus; neither does it furnish any evidence to indicate that such a hypothetic center is localized in the posterior part of the hypothalamus.

10. It may well be that only experiments on man will solve the problem of centers in the hypothalamus for regulating man's vegetative functions. The evidence available either from clinical observations or from animal experiments to date offers no clew as to the relationship between the hypothetic vasomotor center in the hypothalamus or the equally hypothetic dysfunction of this center and the pathogenesis of human "essential" hypertension.

DISCUSSION

DR. LOUIS LEITER: These are experiments on animals only; we hope that some neurosurgeon will have the courage or temerity to stimulate the hypothalamus in the human being without anesthesia.

DR. LEWIS J. POLLOCK: In experiments employing the introduction of drugs in direct contact with the central nervous system, pharmacology should be applied, with the idea in mind that drugs acting only peripherally on the autonomic nervous system should not be expected to have any central action when injected intravenously; if such action occurs, it must be the result of other factors. In connection with respiration, the work of Davis and myself with picrotoxin is of interest. This drug produces apnea an appreciable time before the onset of the convulsive seizure. Regularly a period of hyperpnea is produced, which long precedes the apnea. This can be stopped immediately by decerebration at the level of the colliculi, which shows that there is a secondary center above them. It has long been known that changes in respiration, circulation, secretion and involuntary muscles often occur preceding experimental and spontaneous convulsions.

A COMPARISON OF THE VISCOSITY OF MUSCLES IN CATATONIC AND PARKINSONIAN RIGIDITY

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Many observers have pointed out resemblances between catatonia and the residuals of epidemic encephalitis (Laignel-Lavastine and Logre,[1] Kahn,[2] Rogues de Fursac [2] and Dide, Guiraud and Lafage [3]). Bostroem,[4] Schilder [5] and others have contributed important evidence on the differences between these conditions.

Pathologic studies of the brain in dementia praecox have frequently failed to disclose any differences from the normal brain. Consistent pathologic changes have not been demonstrated. Evidence of lesions in the basal ganglia was reported by Kleist,[6] Steiner,[7] Guiraud,[8] Reiter,[9] and Fränkel.[10] Reports were also made of involvement of other parts of the brain (Josephy,[11] Steck [12]).

From the Department of Nervous and Mental Diseases, Northwestern University Medical School and the Elgin State Hospital.

1. Laignel-Lavastine and Logre: Hébéphréno-catatonie et encéphalite léthargique, Encéphale **15**:473, 1920.

2. In discussion on Claude, H.: Suites éloignées de certains troubles mentaux postencéphalitiques, Ann. méd. psychol. **1**:246, 1922.

3. Dide, Guiraud and Lafage: Syndrome parkinsonien dans la démence précoce, Rev. neurol. **28**:692, 1921.

4. Bostroem: Striäre Störungen, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1926, vol. 2.

5. Schilder, P.: Einige Bemerkungen zu der Problemsphäre: Cortex, Stammganglien-Psyche, Neurose, Ztschr. f. d. ges. Neurol. u. Psychiat. **74**:454, 1922.

6. Kleist at first placed the pathologic changes of catatonia in the frontopontocerebellar system, but later also included the striatum. (Kleist: Die psychomotorischen Störungen und ihr Verhältnis zu den Motilitätsstörungen bei Erkrankungen der Ganglien, Monatschr. f. Psychiat. u. Neurol. **52**:253, 1922.)

7. Steiner: Encephalitische und katatone Motilitätsstörungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **78**:553, 1922.

8. Guiraud, P.: Conception neurologique du syndrome catatonique, Encéphale **19**:571, 1924.

9. Reiter: Extrapyramidal Motor Disturbances in Dementia Praecox, Acta psychiat. et neurol. **1**:287, 1926.

10. Fränkel, F.: Ueber die psychiatrische Bedeutung der Erkrankungen der subcorticalen Ganglien und ihre Beziehungen zur Katatonie, Ztschr. f. d. ges. Neurol. u. Psychiat. **70**:31, 1921.

11. Josephy: Beiträge zur Histopathologie der Dementia Praecox, Ztschr. f. d. ges. Neurol. u. Psychiat. **86**:391, 1923.

12. Steck, H.: Les syndromes extrapyramidaux dans les maladies mentales, Schweiz. Arch. f. Neurol. u. Psychiat. **20**:92, 1926.

The clinical differences between the rigidity in the two conditions have been pointed out by Bostroem,[13] among others. Clinically, it appears to me that on passive movement of the rigid extremity of a catatonic patient an active resistance is encountered. I have the impression that not only passive muscle tension but also voluntary contraction is elicited. Moreover, catatonic rigidity may disappear for a longer or shorter time for no known reason. It may be replaced by a transient hypotonia. (This is shown in the tension curves of a catatonic patient obtained several minutes apart [fig. 1]. There were alternating hypertonia and hypotonia while the tracings were taken.) Such variations in parkinsonian rigidity are found associated with certain recognizable stimuli, and have given rise to the descriptive term akinesia paradoxale.

Claude, Baruk and Thévenard [14] have found differences between the postural reflexes of catatonia and chronic encephalitis. In the normal subject, dorsal flexion of the foot is accompanied by a short and tran-

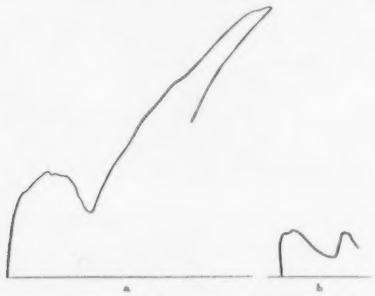

Fig. 1.—Velocity curves showing alternating hypertonia and hypotonia. Tracing *b* was taken several minutes after tracing *a* from the same patient in one sitting.

sient elevation of the tendon of the tibialis anticus—a rise which is translated graphically by a parabolic curve. In parkinsonism, on the contrary, the rise of the tendon of the tibialis anticus is extremely, and sometimes almost indefinitely, prolonged. This is shown in the curves by a rise, followed by a prolonged straight line or a very retarded descent. The curves in catatonia are said by these authors to be variable in character and not affected by scopolamine—a drug which has a pronounced effect on the curves in parkinsonism. They cite also differences in the action current curves in the two diseases, the action current curves in catatonia possessing only the characteristics of a voluntary contraction.

13. Bostroem: Katatone Störungen, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1926, vol. 2.

14. Claude, Baruk and Thévenard: Le syndrome de la démence précoce katatonique, Encéphale **22**:741, 1927.

Pollock and Davis,[15] by recording velocity curves and viscous-elastic flow of muscles of patients suffering from parkinsonism, found that the muscles had a high degree of viscosity and internal friction (fig. 2). The viscosity was reduced to normal by the administration of scopolamine hydrobromide. It was, therefore, thought that a comparison with similar curves obtained from patients with catatonia would help to determine whether any support would be added to the conception that there is some, perhaps psychophysiologic, blocking at the level of the basal ganglia.

Hill [16] found that when a muscle was permitted to shorten and lift a weight, it was unable even to approximate the maximum of work calculated on the theory that muscle is an elastic body. Hartree and Hill [16] found that when the muscle was stretched, a large irreversible production of heat resulted. They concluded that the reason a muscle is incapable of transforming its elastic energy into work is that the frictional and viscous resistances associated with the shortening process cause a large irreversible dissipation of energy. Gasser and Hill [16]

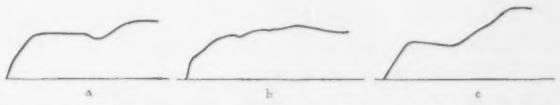

Fig. 2.—"Curves obtained from subjects with chronic encephalitis; note the absence of the dip or diminution in its depth." [15] Compare with curves in figure 3.

found that the force exerted by a muscle decreases as the speed of shortening increases. They also observed that when a muscle is released at the height of a tetanic response to a slightly shorter length, the tension falls quickly toward zero instead of becoming of the magnitude corresponding to its new length. There then follows a slow redevelopment of a curve similar to that of the original tension development. This was interpreted as due to the fact that the contractile elements, in order to regain the tension of the new length, must overcome the internal frictional forces which they had originally to overcome when the tetanus was first developed.

This conception of viscosity, as formulated by Hill, is not identical with the meaning conveyed by the term simple physical viscosity. The development of contraction is accompanied by the formation of some molecular pattern in the muscle fiber which is analogous to a process of crystallization. When a muscle is shortened, the tension developed

15. Pollock, L. J., and Davis, L. E.: Relation of Modifications of Muscle Tonus to Interruption of Certain Anatomic Pathways, Arch. Neurol. & Psychiat. **28**:586 (Sept.) 1932.

16. Quoted by Fulton, F. J.: Muscular Contraction and the Reflex Control of Movement, Baltimore, Williams & Wilkins Company, 1926.

depends on the rearrangement of its elements. This is not an instantaneous process. Thus it is not gross but molecular viscosity that is involved.[17]

The clinical method used in this study of muscle viscosity is that described by Pollock and Davis;[15] it is based on the principle of the development of velocity by movable bodies when put into motion by quickly imparted force. A description of the apparatus, which was constructed by Dr. L. C. Hutchinson of the University of Minnesota, has been given by Pollock and Davis and will not be repeated here. The motor was so geared that a speed of 16.47 revolutions per minute was attained. The patient was seated in a comfortable chair with the right forearm resting on the armboard and forming an angle of 90 degrees with the upper part of the arm. The upper part of the arm made an angle of 10 degrees with the horizontal. The movement of the extremity was recorded in the tracing in a horizontal direction, and the tension developed in a vertical one.

The muscle tension curves were obtained only from patients with catatonic rigidity. In addition to the rigidity, all had other classic symptoms of the disease. All were mute and negativistic in varying degrees. In keeping with the psychosis, they were extremely uncooperative in the procedure. The patient had to be seated forcibly on the chair and his arm placed on the armboard repeatedly before a tracing meeting the requirements of the technic as to position of arm and body could be obtained. After several attempts the patient became accustomed to the procedure and the arm would remain on the armboard without the observer's interference. Obviously, verbal commands to the subject were futile.

Interpretation of the curves is based on the application of the principles of physics to force, velocity, mass and inertia involved in this investigation. "A rapidly moving force acting against a rigid body rotating about a fixed axis by means of a spring must overcome mass and inertia since velocity is being imparted. If the tension of the spring be recorded, it will be found that there will be a more or less immediate rise in tension until movement occurs, which will then be sustained until the moment of greatest velocity, when the velocities of the movable body and the moving force are equal, and then it will rapidly fall toward zero producing the dip alluded to in the following paragraphs.[15]

"If the movement of the rotating body be opposed by a resisting force of a spring or other elastic body, the tension curve will be a composition of the inertia curve and that of a spring"[15]—a curve in which a dip is shown (elasticity).

17. The term "viscosity" employed in this communication as relating to muscle tone is limited to the meaning given to it by Hill[16] and Pollock and Davis.[15]

"A tracing of a weight resting on the armboard whose movement is opposed by a thin walled rubber tubing filled with Chatterton's mixture or with pitch"[14]—this is a curve in which a dip is absent. Internal friction (viscosity) impedes the velocity of the movable body so that a dip is not developed on the tracing. The term viscosity, as already implied in the discussion of Hill's work, is distinctly applied to molecular friction in the sense of internal resistance. In this sense there is, even in elastic solids, a molecular friction. Owing to internal friction, the moment of equal velocity may occur slowly or may never be reached within the limit of movement. When the internal friction is overcome,

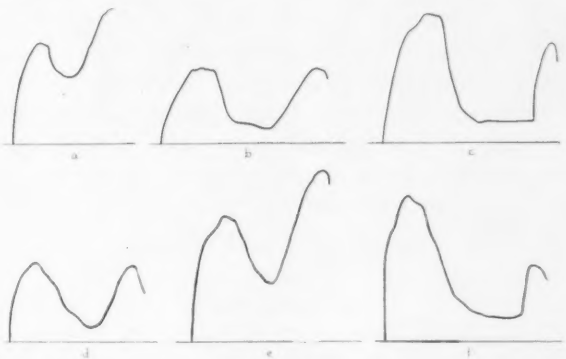

Fig. 3.—Velocity curves obtained from subjects with catatonic dementia praecox. Note the dip that results from the extension of muscles in catatonic rigidity.

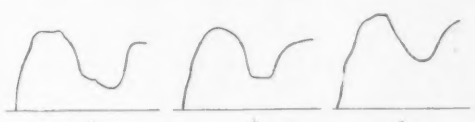

Fig. 4.—Velocity curve showing the dip that results from the extension of normal muscle. Note the similarity to curves in figure 3.

velocity is developed and there is a turning point in the tension. This turning point is shown graphically by the dip in the tracing. The dip is due to the turning point in tension.

Therefore, when a tension curve of the force necessary rapidly to move a rigid body shows a dip, it is the result of the development of velocity. If the movement of the rigid body were opposed by a viscous substance, such a dip would be absent or greatly reduced, whereas resistance by an elastic substance would cause the dip to appear.

Figure 3 shows some muscle tonus curves obtained from catatonic patients. The dip is present in all the curves in varying degrees. The presence of the dip identifies these curves with those obtained with this apparatus from a relatively rapid movement of the armboard, bearing a

weight of about 5 pounds, resisted by a spiral spring, and with the curves obtained of the flexion or extension of the forearm of normal adults (fig. 4). The curves are also similar to tracings obtained from patients suffering from interruptions of the corticospinal tract. In all of these tracings, velocity is developed, and a turning point in tension causes a dip indicating a high degree of elasticity and but little internal friction. On analysis, the curves are seen to be of an inertia-elastic composition and obey Hook's law. The end-loops of the curves are formed when the tension on the armboard is removed at the same rate of speed as it was applied. These are called hysteresis or lag loops. They are due to the lag of the arm on returning to the original position when tension is removed. The hysteresis loops are not considered critical in these curves. They would not indicate the degree of viscosity of the muscle because voluntary and other motor components influenced by the personality of the patient participate in the formation of these loops. The arm of the catatonic patient may voluntarily be held in extension when the force is removed. In nonpsychotic patients these loops are of significance; for example, in chronic encephalitis the loops are very large, indicating great internal friction.

CONCLUSION

1. The muscles of patients suffering from catatonic dementia praecox possess a high degree of elasticity and but little internal friction (viscosity).

2. Catatonic rigidity differs in this respect from the rigidity of chronic encephalitis. "The muscles of patients suffering from Parkinsonism possess both high internal resistance of so-called viscosity and a large viscous-elastic flow."[15] The difference between the muscle tonus curves of chronic encephalitis and catatonia is evidence that the muscle rigidity in these two conditions is not due to physiologic interruption at the same levels.

NATURE AND ORIGIN OF SOME TUMORS OF THE CEREBELLUM

MEDULLOBLASTOMA

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At the meeting of the New York Neurological Society in March, 1931, one of us (L. S.) described [1] two tumors of the cerebellum which we believed were derived from the granular layers and were therefore probably neuroblastomas, since the external granular layer of the cerebellum is composed, as far as we know, only of neuroblasts. These two tumors had been previously classified as medulloblastomas, since they fitted the description of such tumors very well. Since then, we have found another such tumor at Bellevue Hospital and have been enabled by Dr. Karl Rothschild, of New Brunswick, N. J., to study another. Dr. Walter Dandy, of Baltimore, has allowed us to study sections from two other cerebellar tumors which we believe also may be classified in this group. In this paper, therefore, we describe six tumors of the cerebellum which we think should be called neuroblastomas and, since they are in our opinion derived from the granular layers, we have suggested the name of granuloblastomas for them.

Whether other medulloblastomas may be derived in the same manner is a question of some interest. After all, the medulloblast is a hypothetic cell. Indeed, Percival Bailey, who in 1925 suggested the name "medulloblastoma" for a certain type of tumor of the cerebellum, said in one paper,[2] "especially hypothetic are the medulloblasts" and, later, "the component cells of the medulloblastoma for the most part do not have morphologic characteristics that can be sharply displayed by special staining methods." Bailey derived from the medulloblast not only the tumors he called medulloblastomas, but also the oligodendroglia cells of

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Read by title at the Fifty-Ninth Annual Meeting of the American Neurological Association, Washington, D. C., May 10, 1933.

1. Stevenson, Lewis: Tumors of the Cerebellum, Arch. Neurol. & Psychiat. **26**:875 (Oct.) 1931.

2. Bailey, P.: Histologic Atlas of Gliomas, Arch. Path. **4**:872 (Dec.) 1927.

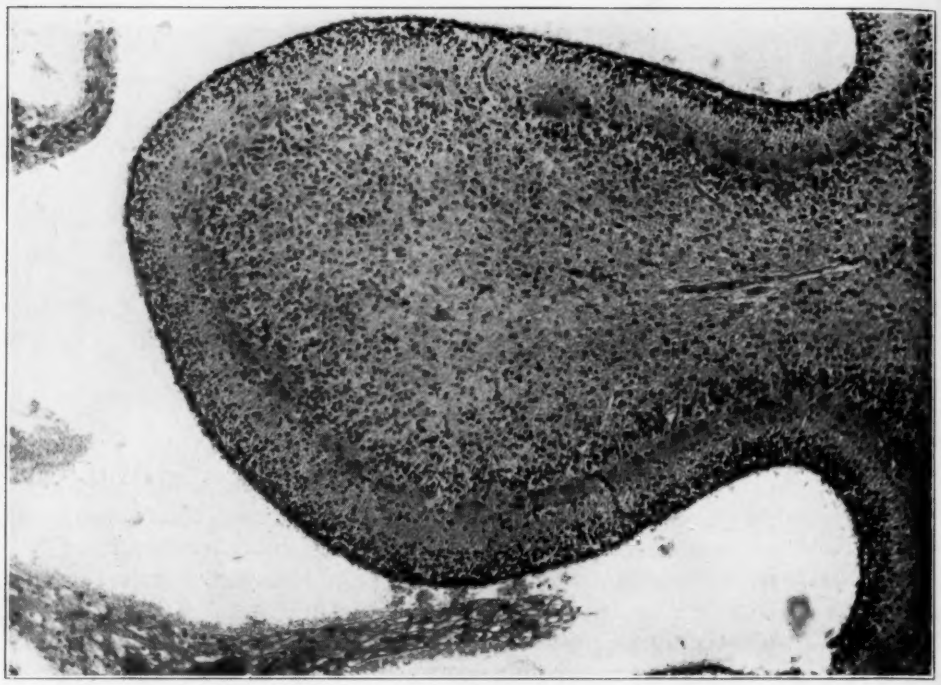

Fig. 1.—Cerebellum of a human fetus of about 6 months, showing the outer layer of granule cells with the incompletely developed inner granular layer. Low power magnification. Hematoxylin and eosin stain.

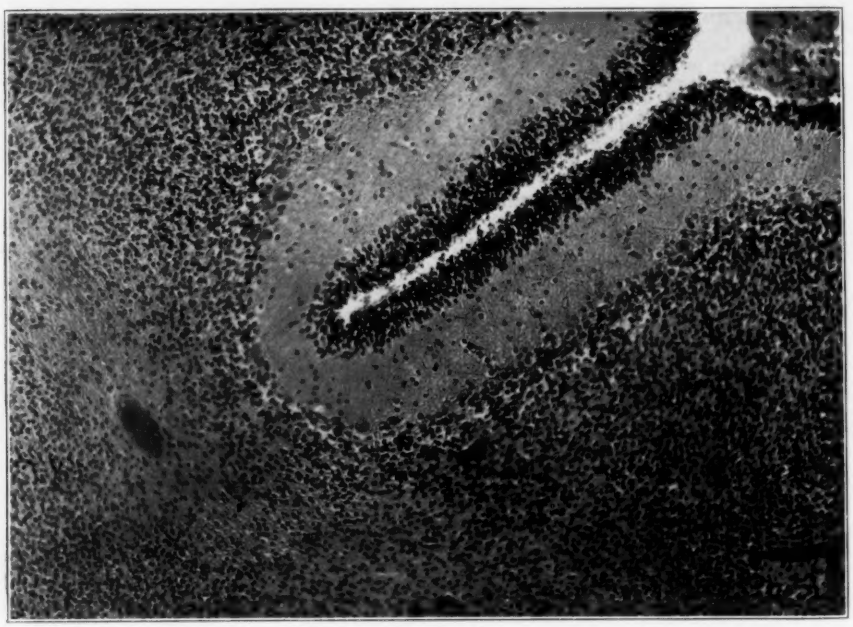

Fig. 2.—Cerebellum of a new-born child, showing the thick external layer of granule cells. Hematoxylin and eosin stain.

the nervous system. Del Rio Hortega, in a recent paper [3] on the oligodendroglia, said that he did not believe that these cells are derived from medulloblasts or indifferent, bipotential cells, but directly from the gliocytoblasts.

The whole question so far has rested on Schaper's hypothesis [4] that all of the germinal cells in the medullary epithelium of the embryo do not form nerve cells, as suggested by His and Cajal, but that some remain indifferent and are bipotential; that is, have the power later to develop into either neuroblasts or spongioblasts or, indeed, to remain

Fig. 3.—Cerebellum of a child 11 months old, showing the external granular layer still present. Hematoxylin and eosin stain.

indifferent. These hypothetic, indifferent, bipotential cells (medulloblasts) have been supposed to give rise to tumors and malformations of the brain.

If one studies microscopic sections of the cerebellum in a human fetus at different ages and, indeed, in children up to the age of 1 year or more, it can be seen clearly that the granular layer occurs at first mostly on the outer surface of the leaflets. As the child develops, this

3. del Rio Hortega, P.: The Morphology and Functional Interpretation of the Oligodendroglia, Mem. d. Soc. españ. hist. natur. **14**:5, 1928.

4. Schaper, A.: Die frühesten Differenzierungsvorgänge im Centralnerven-System, Arch. f. Entwcklngsmechn. **5**:81, 1897.

layer of cells migrates inward to the position seen in adult life. Compare figures 1, 2 and 3, which are photomicrographs from some of our own preparations of the developing cerebellum in man. As Cajal has shown,[5] the outer granular layer (Obersteiner's layer) is composed of round, undifferentiated cells without processes, which become somewhat

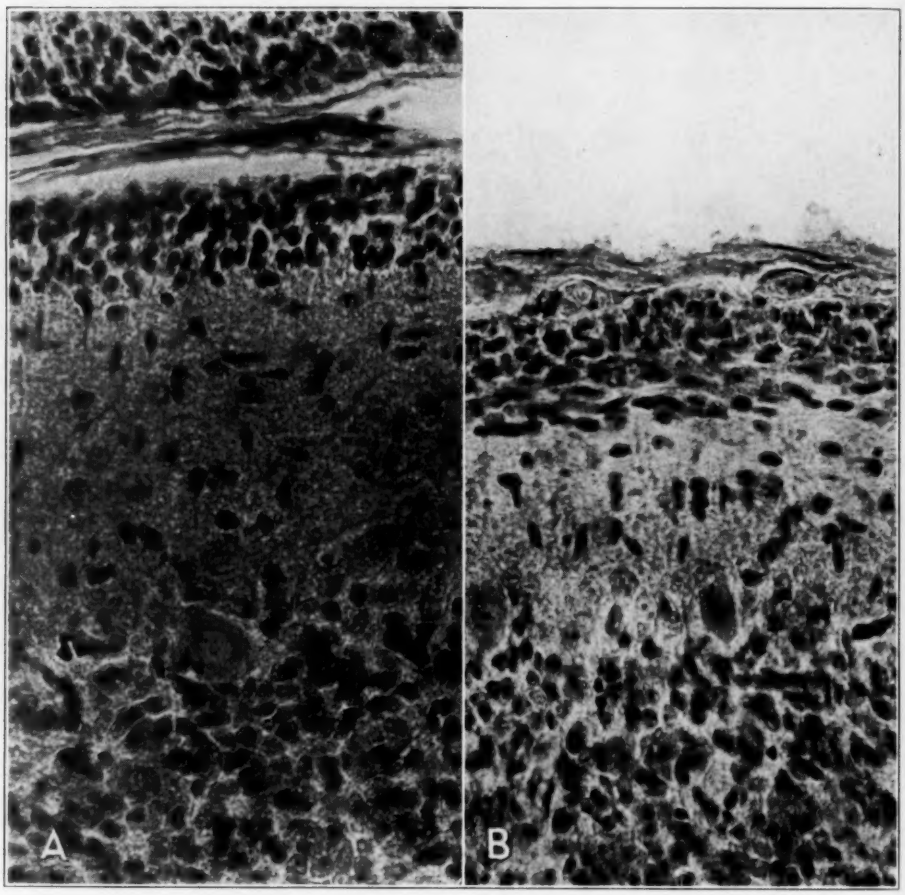

Fig. 4.—Cerebellum of a kitten 3 days old. Silver carbonate stain. *A* shows the difference in size of the granule cells in the external layer compared with those of the internal layer. *B* shows round and oval nuclei in the external granular layer and granule cells migrating from the external to the internal layer.

elongated and disposed longitudinally and, later, arranged vertically as they pass through the molecular layer of the leaflet to gain their final position as the adult neurons of the internal granular layer with an

5. Ramón y Cajal, S.: Histologie du système nerveux de l'homme et des vertébrés, Paris, A. Maloine, 1909, vol. 2, p. 80.

axon which penetrates nearly to the outer surface of the leaflet (fig. 4). Among these changing cells mitotic figures can be seen, as in figure 5. Such cells, at first undifferentiated, rapidly dividing and changing both their shape and their position, might easily be supposed to give rise to tumors.

REPORT OF CASES

CASE 1.—Figure 6 illustrates the gross appearance of the first tumor of our series. Mrs. A. B., a woman aged 29, complained of occipital headaches for

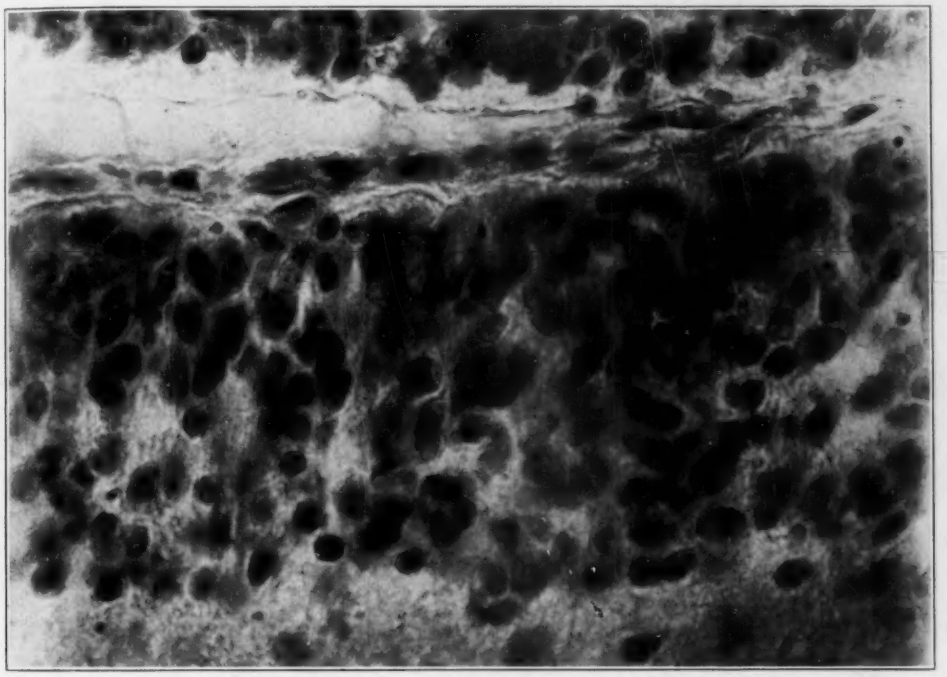

Fig. 5.—Cerebellum of a kitten 3 days old, showing the external granular layer with mitotic figures. Some cells are much larger than others. Silver carbonate stain.

two months before admission to Belleuve Hospital (service of Dr. Foster Kennedy), with blurring of vision for one month. She also suffered from vomiting and dizziness and a tendency to fall backward. Speech later became disturbed, and she had ataxia of the arms. She had choked disks and a fine horizontal nystagmus. There was no Babinski sign. The illness lasted about three months. She was operated on and died.

At autopsy, a tumor was found in the cerebellum, extending 2 cm. to the left of the midline and 3 cm. to the right. The growth was described as soft, somewhat cystic and a light yellow. The brain was fixed in formaldehyde bromide.

Figure 7 shows a section of the cerebellum near the edge of the tumor. In this figure one can see tumor cells apparently growing from the outer surface

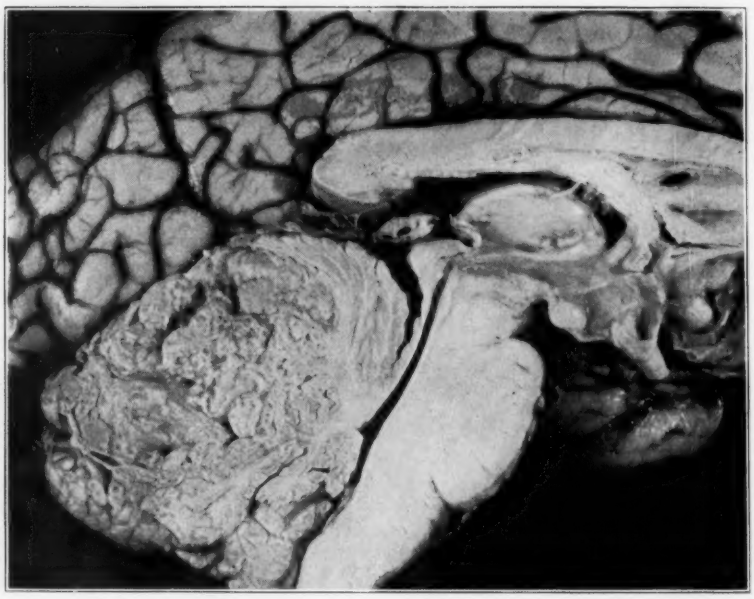

Fig. 6 (case 1).—Gross tumor, showing midline position of the tumor in the vermis of the cerebellum. The tumor does not grow from the roof of the fourth ventricle.

Fig. 7 (case 1).—View of the cerebellum with a tumor mass growing from the external granular layer of the cerebellum and spreading the leaflets apart (top). At the bottom can be seen normal cerebellum. Hematoxylin and eosin stain.

of the leaflets and separating them. It was this peculiar appearance that first focused our attention on this tumor as being in some way peculiar and different from other gliomas of the cerebellum. In some parts of this cerebellum, adjacent to the tumor, there is what appears to be a remnant of an external granular layer (layer of Obersteiner). The cells are six or seven rows deep in places, and in size, shape and staining characteristics closely resemble the cells of the internal granular layer—they appear, indeed, to be the same cells. In other regions this external layer of granule cells has widened out and has become merged with a mass of cells constituting the tumor and separating adjacent leaflets. In many leaflets of the cerebellum the cells from this external granular layer are seen to be

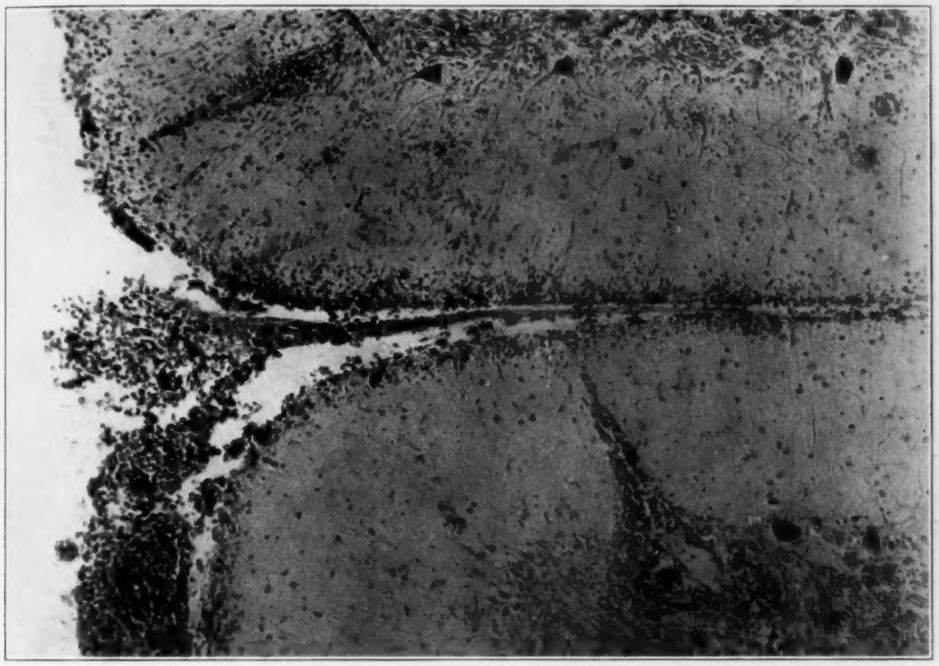

Fig. 8 (case 1).—Vestigial remains of the external granular layer seen on the outer surface of two leaflets. This can be seen to grow into a tumor mass at the left of the figure. Cells can also be seen streaming inward from the external granular layer to the internal layer and not confined to the spaces about blood vessels. Nissl stain.

migrating inward and to become lost in the internal granular layer, as they do in the normal development of the cerebellum. At times they migrate along the outside of blood vessels, but not always, since the molecular layer of the leaflet can be seen to be studded with hundreds of migrating cells on their way inward independently of any vessels. These appearances can be seen in part in figure 8. As the cells leave the external surface of the leaflet and multiply to form the tumor mass, they seem to become less rounded and often larger. Like the normal granular cells, they have little cytoplasm, and no fibrils of any kind could be demonstrated by the reduced silver methods of Cajal, del Rio Hortega's silver carbonate, phospho-

tungstic acid-hematoxylin or Bielschowsky's method for blocks of tissue. The nature of the cells seems best demonstrated by the Nissl preparations. There was a well developed stroma in this tumor which was readily stained by del Rio Hortega's modification of his silver carbonate stain for connective tissue. Figure 11 shows the stroma very well. Only a few mitotic figures can be seen in the tumor.

CASE 2.—G. B., a Negro boy, aged 16, complained of occipital headache for four weeks on getting up in the morning. The headache became worse on walking or working. He had choked disks and occasional vomiting; there was no Babinski sign. He had some stiffness of the neck and held his head backward and to the

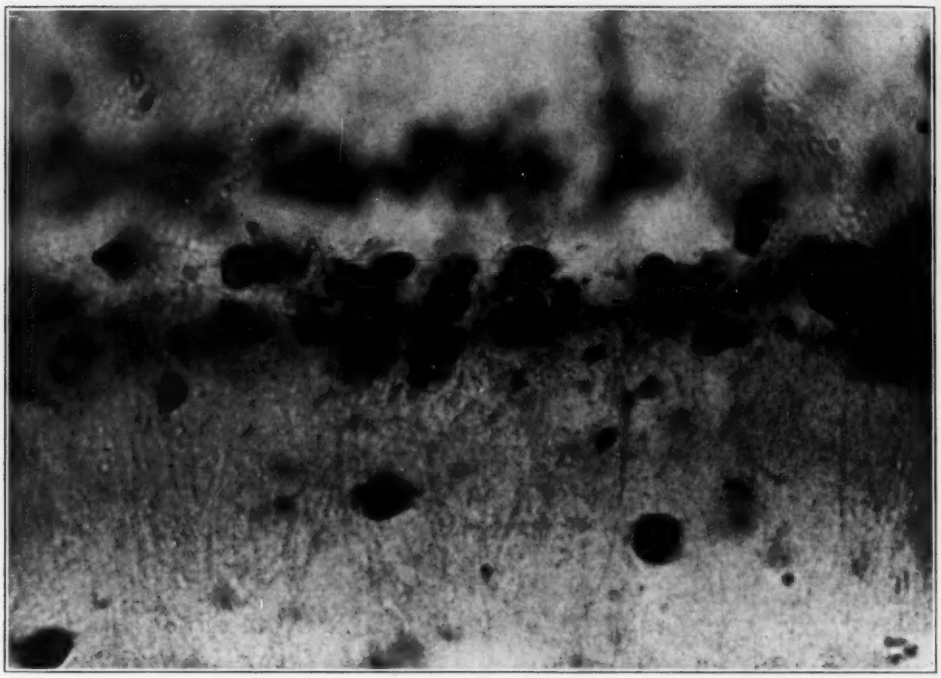

Fig. 9 (case 1).—View of the external granular layer illustrated in figure 8, to show appearance of the cells and their resemblance to granule cells. Oil immersion. Nissl stain.

left. He had slight ataxia of the arms and legs. He was ill for about two months altogether and died suddenly after a general convulsion.

Autopsy revealed a marked internal hydrocephalus, with a large, mottled grayish tumor in the right hemisphere of the cerebellum. The brain was fixed in formaldehyde bromide. Figure 12 shows a low power view of the cerebellum adjacent to the tumor. Again one can see the peculiar way in which the tumor cells seem to be growing from the external surface of the leaflets and pushing them apart. This tumor, like the first one, is composed largely of cells which have round or slightly oval nuclei and little cytoplasm. The cells resemble granule cells, with a central nucleolus and rather light-staining nucleus. They are, for the most part, considerably larger than normal granule cells in the body of the

Fig. 10 (case 1).—Tumor cells are shown streaming in from the external to the internal granular layer, not only along the perivascular spaces but also independently of any vessels, just as in the normal development of the cerebellum. The blood vessels at the right have no tumor cells growing from them as in perithelial sarcomas. Hematoxylin and eosin stain.

Fig. 11 (case 1).—Rather abundant stroma with tumor cells in its spaces. Del Rio Hortega's silver carbonate stain for connective tissue.

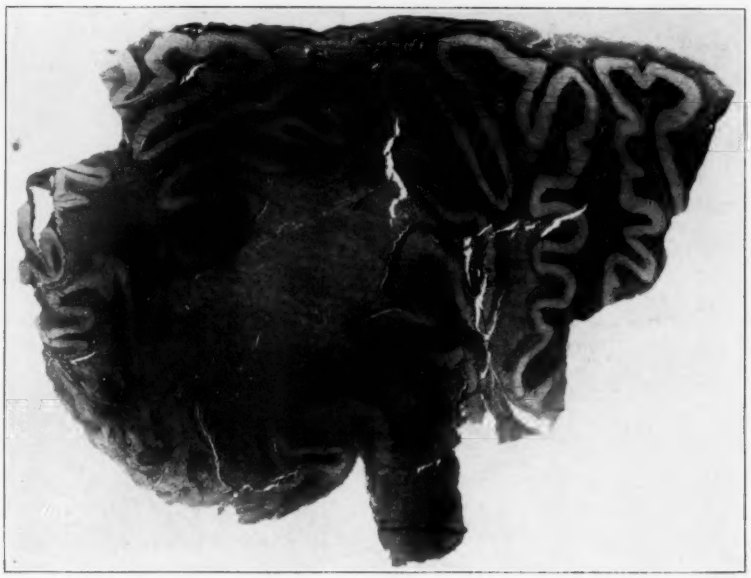

Fig. 12 (case 2).—View of cerebellum to show separation of the leaflets by a tumor growing from the external granular layer as in figure 7. Hematoxylin and eosin stain.

Fig. 13 (case 2).—Tumor cells arising in the external granular layer and tumor extending into the internal granular layer along a vessel. Hematoxylin and eosin stain.

tumor. Again, however, if one studies the tumor cells at the outer margin of a leaflet, many cells identical with granule cells can be seen. Lying among these larger tumor cells can be seen in this case hundreds of small round cells, darkly stained and resembling lymphocytes, with no demonstrable cytoplasm or like the more darkly staining of the normal granule cells. The nature of the cells is most clearly seen in the Nissl preparations, just as in the first tumor. No fibrils could be stained in this tumor by any of the methods mentioned. There is a stroma much like that of the first tumor, but somewhat finer in texture. This stroma does not seem to radiate from blood vessels or to form rings about them, as in the case of many of the sarcomas. It forms a rather complicated wavy pattern, including tumor cells within its different sized spaces. Blood vessels are fairly numerous, and some of them have a moderately thick wall, but seem otherwise to be normal. Figure 13 shows this tumor growing from the outer surface of the cerebellar leaflet and penetrating to the internal granule layer along a blood vessel.

CASE 3.—This case was studied and personally described by Dr. Karl Rothschild.[6] The tumor occurred in a boy, aged 6 (J. K.). Examination showed the head to be very large, and there was slight stiffness of the neck. The deep reflexes in the arms were not very active; the abdominal reflexes were absent. A slight Babinski sign was present on the right, and there was a suggestion of a Kernig sign. There was no ataxia or nystagmus. The cranial nerves were normal, except for bilateral papilledema with some pallor of the left optic nerve, blindness of the right eye and marked loss of vision in the left.

At autopsy, a tumor about the size of a small hen's egg was found in the middle line of the cerebellum. It had a spongy appearance and was somewhat hemorrhagic. The brain was fixed in formaldehyde. A part of this tumor was given to us for study. It differed from the first two tumors in some ways—for example, it had very little stroma. However, it would be considered, we believe, a typical medulloblastoma. It was composed of small cells with round, slightly oval or carrot-shaped nuclei, with no stainable cytoplasm. We could demonstrate no fibrills of any kind within it. In one or two places it seemed to be growing from the outer surface of the cerebellar leaflets, as illustrated in figure 14. At one place in this cerebellum a typical appearance of a vestigial external granular layer could be seen.

CASE 4.—H. G., an Italian man, aged 38, was admitted to Bellevue Hospital in February, 1919. The illness lasted a little over three months. He had severe, right-sided headache and projectile vomiting. There was some rigidity of the neck. At one time the patient's pupils were unequal and sluggish to light, and upward and downward gaze seemed to be greatly impaired. He did not have choked disks. He was irritable and lay curled up on his right side. A diagnosis of epidemic encephalitis was made.

Autopsy revealed a large, soft, mushy tumor involving the cerebellum, more on the left side, but bridging across the middle line and involving the right cerebellar hemisphere also. A pathologist at Bellevue Hospital who examined microscopic sections of this tumor wrote: "The tumor mass is composed of cells bearing a striking resemblance to those of the granular layer of the cerebellum. Morphologically they also resemble lymphocytes." From a study of the

6. Rothschild, Karl: Medulloblastoma Cerebelli: Case with Autopsy; Midline Cerebellar Tumors in Children and Young Adults, Ann. Int. Med. **5**:643 (Nov.) 1931.

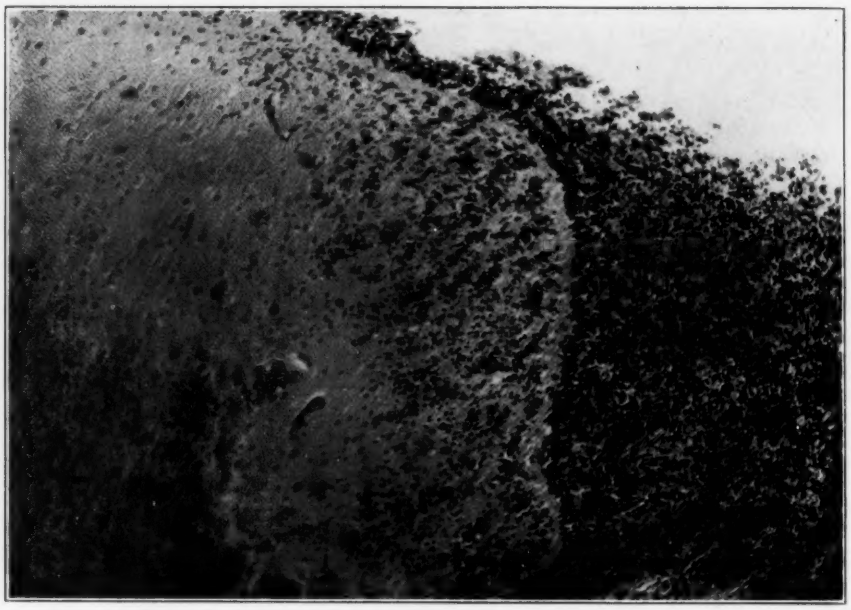

Fig. 14 (case 3).—Tumor cells streaming inward from the external granular layer toward the internal layer. Phosphotungstic acid-hematoxylin stain.

Fig. 15 (case 4).—Tumor growing from an external granular layer of the cerebellum. The peculiar appearance and arrangement of cells in strings and loops seen at the left was present in cases 1 and 2. Hematoxylin and eosin stain.

sections of this tumor stained with hematoxylin-eosin, we believe it to be identical with the first two tumors described, although we had no gross material to work with. The tumor cells follow the blood vessels through the molecular layer of the leaflet from one granule layer to another, in the same manner as in the first two tumors. Moreover, the tumor cells are arranged in peculiar strands and loops, as if lying within the same sort of abundant stroma as that seen in the first two tumors. Again, the tumor cells on the outside of the leaflets resemble closely the normal granule cells, although in the body of the tumor they are a little larger on the average and not always so round. Figure 15 illustrates the appearance of this tumor.

The fifth and sixth cases are from the surgical-pathologic service of the Johns Hopkins Hospital, and we were enabled to study only the sections stained with hematoxylin-eosin, given to us by Dr. W. Dandy. No gross material was available.

CASE 5.—L. F., a white man, aged 21, was admitted to the service of Dr. Dandy on June 7, 1922, because of severe occipital headaches, projectile vomiting, dizziness, blurred vision and irregularity in gait. These symptoms had started ten months previously with early morning headaches and had been progressive in nature. On examination, the patient complained of an accentuation of the occipital headache on movement of the neck. Bilateral markedly choked disks, pronounced horizontal nystagmus, severe Rombergism, ataxia and adiadokokinesis were noted.

Through a cerebellar approach, Dr. Dandy, on June 7, revealed "a very soft tumor occupying the vermis and a considerable part of both hemispheres. On the dorsal aspect of the medulla was a grayish white mass which was well outlined against the surrounding white tissue; it looked like a secondary metastasis."

At one place in the microscopic section of this tumor, the internal granular layer of the cerebellar leaflet is continuous with the tumor tissue and the tumor has the appearance of a continuation of this granular layer. However, the cells in the body of the tumor have more cytoplasm than in other tumors of this series, and it stains fairly well with eosin. The true nature of this tumor, of course, cannot be fully determined, since we have no gross material to work with. However, there seems to be a close connection of the granule cells and the tumor cells.

CASE 6.—R. M., a white man, aged 22, was admitted to the service of Dr. Dandy on Oct. 2, 1921, complaining of severe occipital headaches of one one month's duration. The headaches at first occurred only in the early morning, but soon became almost persistent, confining the patient to bed. Physical examination revealed bilateral papilledema, slight weakness of the left side of the face and forehead, and pain on hyperextension of the neck.

On October 9, Dr. Dandy performed a cerebellar exploration and exposed "a definite tumor which involved the posterior part of the vermis and protruded quite markedly backwards." The tumor, including all that could be seen of the vermis with the posterior-inferior and medial portions of each lobe of the cerebellum in juxtaposition to the vermis, was resected.

Figures 16 and 17 show part of the cerebellum in these two cases, with tumor growing from the outer edge of the leaflets. In figure 17 the appearance in places is that of an external granular layer in a normal new-born child.

Fig. 16 (case 5, Dr. W. Dandy's case).—Cerebellum with tumor cells growing from the external granular layer above and to the left. Hematoxylin and eosin stain.

Fig. 17 (case 6, Dr. W. Dandy's case).—The cerebellum in this case has an external granular layer like that in a normal new-born child. Compare with figure 2. The tumor mass is seen at the left. Hematoxylin and eosin stain.

COMMENT

The six tumors described were entirely confined to the cerebellum. There was no tumor mass in any of the ventricles in the cases of the first two tumors. The question that might be raised about the first, second and fourth tumors is whether they are not examples of primary sarcoma of the brain derived from the leptomeninges [7] or the blood vessels—so-called perithelial sarcomas, peritheliomas or perivascular sarcomas. These three tumors differ from such sarcomas in not having any visible attachment to the external coat of the blood vessels [8] and in the scarcity of their cytoplasm. The stroma of the first two differs from that of sarcomas also; it does not form rings about the vessels [9] nor does it envelop the cells close to the vessels. There were no areas of necrosis in these tumors, as is so characteristic of peritheliomas. Rather, the cells resemble in morphology and behavior the cells of the external granular layer of the infant cerebellum, migrating inward through the molecular layer of the leaflets, and also forming tumor and pushing the leaflets asunder.

If medulloblasts do occur in the nervous system, there seems to be no good reason why they should be confined to the cerebellum or to the roof of the fourth ventricle and produce tumors almost invariably in the cerebellum. The very few tumors with a histologic structure similar to medulloblastomas which have been found elsewhere (only two in Cushing's series),[10] might well enough be neuroblastomas or oligodendrogliomas or some other form of tumor. It also seems to us that the finding of a few cells in medulloblastomas which resemble either neuroblasts or spongioblasts is not sufficient evidence on which to base the theory that the type cell of which the medulloblastoma is composed is, therefore, a bipotential cell and capable of producing both neuroblasts and spongioblasts. It has seemed to us for some time that it is difficult to tell the difference between neuroblasts and spongioblasts in their early stages unless one can actually see Nissl substance or definite neurofibril formation within the cell. The reduced silver method of Cajal and the silver carbonate method of del Rio Hortega or even the gold sublimate method of Cajal are not specific enough to enable us certainly to identify the earlier stages of the cells that go to make up the nervous system, especially when these are found in masses of tumor cells.

7. Ford, F. R., and Firor, W. M.: Primary "Sarcomatosis" of the Leptomeninges, Bull. Johns Hopkins Hosp. **35**:69, 1924.

8. Stevenson, L. D., and Hyslop, G. H.: Perithelioma of the Brain, M. Clin. North America **14**:451, 1930.

9. Bailey, P.: Intracranial Sarcomatous Tumors of Leptomeningeal Origin, Arch. Surg. **18**:1359 (April) 1929.

10. Cushing, H.: Experiences with the Cerebellar Medulloblastomas, Acta path. et microbiol. Scandinav. **7**:1, 1930.

On the other hand, if the tumors we have described arise from a specific cerebellar structure, it explains more readily why they are confined so largely to the cerebellum. Again, if they come from the external granular layer of the cerebellum, it is easy to see why cells resembling neuroblasts should be so often found in them, since the external granules are neuroblasts or, at least, predominantly so. Of course, it is still possible that Cajal is wrong in supposing that none of the neuroglia cells in the cerebellum come from the external granular layer. The neuroglia cells of the cerebellum are believed by Cajal to be derived in the same way as those of the medulla and spinal cord, namely, from ependymal cells about the central canal. We believe that if a definitely gliomatous type of tumor were seen to arise from the external granular layer of the cerebellum, it would be a better proof of Dr. Bailey's hypothesis of the medulloblastoma [11] than the finding of a few neuroblasts and spongioblasts in medulloblastomas. This would show that spongioblasts can be produced from Obersteiner's layer which, without doubt, is now known to produce the neuroblasts which finally develop into the various neurons of the cerebellum, although the origin of the Purkinje cells is not yet definitely known.

In the child of 6 months or more, the cells of the two granular layers of the cerebellum are much alike in size and staining properties and are, for the most part, round. In the fetus of 3 to 4 months, the cells of the external granular layer are not quite so round and uniform as those of the internal layer. In lower animals, like the cat, the two layers are not quite the same in appearance. In the kitten of 2 or 3 days, the external layer of cells is smaller and more darkly staining than those of the internal granular layer (compare cells in figure 4, using a magnifying glass). In the kitten, also, two kinds of cells can be seen in the external granular layer. Those most externally are round and those deeper down are placed horizontally and are elongated, as demonstrated previously by Cajal. In the guinea-pig, the granule cells often appear to have two nucleoli instead of one. The differences seen in the normal development of these cells in man and lower animals seem to us to warrant the assumption on our part that the cells in our tumors may vary a little in size and staining properties, as we have described, and still be granule cells. It is difficult to demonstrate the dendrites or axons of normal granule cells in young animals except by such stains as Golgi's. It is not surprising, then, that we find no fibrils or processes growing from the cells of our tumors. Of course, the granule cells of Obersteiner's layer have no processes of any kind until they begin to migrate inward. If, then, as we suppose, our tumors are composed of

11. Bailey, P., and Cushing, H.: Tumors of the Glioma Group, Philadelphia, J. B. Lippincott Company, 1926, p. 28.

the indifferent or early stage of the granule cell, there would be no processes or fibrils to stain even by Golgi's method.

It is further emphasized that the cells of the medulloblastoma have a tendency to form balls or rosettes. This is quite true, but it is also a tendency shared by the internal granular cells of the cerebellum to a remarkable degree.

Medulloblastomas are often described as "reddish gray" (Bailey).[12] Of interest in this respect is Obersteiner's observation that the granular layer of the cerebellum is "rust colored."[13]

12. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933, p. 227.

13. Obersteiner, H., and Hill, A.: The Anatomy of the Central Nervous Organs, London, C. Griffin & Co., 1890, p. 323.

CEREBELLUM AND RED NUCLEUS

A PRELIMINARY REPORT ON A NEW METHOD OF PHYSIOLOGIC INVESTIGATION

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The greatest difficulty of the experimental neurologist is to present the results of his researches so convincingly that not only will they be accepted by those who are favorably disposed, but that it will not be possible for any one not to accept them.

This applies particularly to the investigation of function in the cerebellum and red nucleus. And the fact that so many methods have been tried by different observers without definite results only strengthens the stand of the unbelievers. Nevertheless all of these experiments have added something to the knowledge, though in no instance has this been conclusive. The experiments of Magnus [1] and de Kleyn on thalamus and decerebrate animals can at best show only what activities remain after the forebrain and part of the midbrain have been removed. The extremely interesting results of Rademaker [2] are for similar reasons open to question. In localized ablations the same doubt arises.

Small lesions confined to nuclei, e. g., the cerebellar nuclei and the red nuclei, have in my experience produced no results, excepting in one instance. Having failed to obtain symptoms when the lesion involved the posterior region of one red nucleus and again when the same parts in both red nuclei were destroyed, the effect of a lesion in the anterior portion of the left nucleus was tried. In this case something definite was observed, for on the following day the animal was found in a sitting posture with the head, body and tail curved to the right, and on moving it turned in circles to the right, pivoting on its hindlegs. All righting reflexes were lost for the first few days, but the reflex from the right side did not reappear until the second week.[3]

Large lesions, on the other hand, which cause almost complete destruction, as in Ingram and Ranson's [4] experiments on the red nuclei,

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Read at the Fifty-Ninth Annual Meeting of the American Neurological Association, Washington, D. C., May 9, 1933.

1. Magnus. R.: Körperstellung, Berlin, Julius Springer, 1924.
2. Rademaker, G. G. J.: Das Stehen, Berlin, Julius Springer, 1931.
3. Mussen, A. T.: Experimental Investigations on the Cerebellum, Brain **50**:313, 1927.
4. Ingram, W. R., and Ranson, S. W.: Effects of Lesions in the Red Nuclei in Cats, Arch. Neurol. & Psychiat. **28**:483 (Sept.) 1932.

have produced some results, but nothing of a decided character. The animal was still able to walk and right itself, but the gait showed dysmetria and ataxia. It is to be regretted that this series of experiments did not include the complete destruction of one of the nuclei so that the unrestrained activity of the other could have been observed.

The results obtained by stimulating the deeper structures of the brain stem have been, as a rule, very unsatisfactory. Previous to the advent of the stereotaxic instrument, it was possible to reach only very indefinite regions in animals that had been subjected to some form of decerebration. The observations of Thiele,[5] Brown,[6] Weed[7] and Környey[8] on the mesencephalic tegmentum were practically similar. All reported ipsilateral flexion and contralateral extension in the forelimbs, while the reaction in the hindlimbs suggested ipsilateral extension and contralateral flexion. The focal point of these responses varied with the observer, the medial nucleus of the thalamus, the red nucleus, the medial longitudinal fasciculus and the substantia nigra being mentioned. With the appearance of the stereotaxic instrument all difficulties connected with the destruction or stimulation of the deeper structures in the brain stem were supposed to vanish. The first experiments by Horsley and Clarke[9] were interesting. They examined the structure and function of the cerebellum and reported that both the cortex and the nuclei responded to the faradic current, though not so actively as the motor cortex. Unfortunately, the second part of their research was never published.

Sachs,[10] employing the same method, investigated the function of the thalamus. He showed that the nucleus anterior gave no response, and that in the dorsal part of the nucleus medius the eyes were dilated and fixed, whereas in the ventral part the head and eyes were deviated to the opposite side, and the opposite forelimb was flexed. In the lateral nucleus, posterior third, dorsal part, the eyes showed conjugate deviation

5. Thiele, F. H.: On the Efferent Relationship of the Optic Thalamus and Deiters' Nucleus to the Spinal Cord, with Special Reference to the Cerebellar Influx Theory of Dr. Hughlings Jackson and the Genesis of the Decerebrate Rigidity of Ord and Sherrington, J. Physiol. **32**:358, 1905.

6. Brown, T. Graham: On the Effect of Artificial Stimulation of the Red Nucleus in the Anthropoid Ape, J. Physiol. **49**:185, 1915.

7. Weed, L. H.: Observations on Decerebrate Rigidity, J. Physiol. **48**:205, 1914.

8. Környey, S.: Experimentalstudien am Nervensystem: X. Tonusänderungen, insbesondere der Rumpfmuskulatur bei Reizung des Mittelhirnquerschnittes, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **30**:120, 1927.

9. Horsley, V., and Clarke, R. H.: The Structure and Functions of the Cerebellum Examined by a New Method, Brain **31**:45, 1908.

10. Sachs, E.: On the Structure and Functional Relations of the Optic Thalamus, Brain **32**:95, 1909.

to the opposite side; in the ventral part the eyes were opened and the limbs showed progressive movements. The dorsal part of the middle third of this nucleus showed flexion and extension of the opposite limbs; in the ventral part progressive movements were observed. Dorsally, the anterior third of the lateral nucleus showed capsular movements; ventrally, the head was turned to the opposite side, the mouth was opened, and the forelimbs and hindlimbs were flexed. Stimulation of the pulvinar resulted in dilation of the pupils and conjugate deviation of the head to the opposite side. While such a varied list of activities is interesting, there is nothing of any decided physiologic importance.

My own experiments on stimulation of the red nucleus gave such negative results that they were not published. But the investigations into the excitability of the cerebellar cortex yielded definite reactions.[11] When the anterior vermis was stimulated the posterior muscles of the neck responded, the head was drawn upward and backward, the forelegs were extended, and the hindlegs were flexed. Excitation of the posterior vermis contracted the anterior muscles of the neck, drawing the head down, flexing the forelegs and extending the hindlegs. The middle lobe of the vermis was concerned with rotation movements. The lateral lobes are in association with the lateral muscles of the neck; the paramedian lobe with the shoulder, forearm and paw; the paraflocculus, anterior, median and posterior divisions, with the hindlimbs, back and forelimbs, respectively. These responses indicated that the lobes were arranged in a definite pattern, those with antagonistic reactions being placed opposite to each other. Such a distribution, if it can be proved to exist, would greatly simplify the understanding of synergic control.[3]

While such localizations were extremely problematic, the arrangement was something definite which future experiments would either support or disprove. To test the corrections of these reactions it was decided to destroy the anterior lobe of the vermis in one cat, and the posterior lobe in another, for it was argued that if the anterior vermis controlled the posterior muscles of the neck, the removal of this influence would disturb forward balance. And if the activity of the posterior vermis was destroyed the anterior muscles of the neck would not respond to correct the disturbed equilibrium, and backward balance would be lost. The result of these operations proved the correctness of the conclusions drawn from the experiments on stimulation.[11]

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11. Mussen, A. T.: The Cerebellum: Comparison of Symptoms Resulting from Lesions of Individual Lobes with the Reactions of the Same Lobes to Stimulation, Arch. Neurol. & Psychiat. **25**:702 (April) 1931.

About this time, Ingram, Ranson and their co-workers [12] became interested in the possibilities of the stereotaxic instrument and undertook the investigation of the mesencephalic tegmentum by the stimulation method. The same tegmental response described by other workers who had stimulated the cut surface of the brain stem was again found, viz., that on the side stimulated the forelimb was flexed and the head and trunk concaved; the contralateral forelimb was extended; the movements in the hindlimbs varied between flexion and extension. These so-called typical responses were found throughout the reticular area in the neighborhood of the red nucleus. But from the red nucleus itself no response was obtained.

Other regions examined included the ventral part of the thalamus, which appeared to be silent. The anterior commissure, the nucleus prethalamicus, the fornix, the olfactohabenular fibers, the nucleus tangentialis, the median part of the globus pallidus, the olfactoseptal fibers and the anterior inferior thalamic pedicle were unresponsive. No reaction was obtained from the nucleus subfascicularis. The ventral part of the nucleus ventralis of the thalamus showed retraction of the nictitating membranes, with dilation of the pupils. In most of the hypothalamic region only the dilation of the pupils was to be observed.

Though all of these various investigations have produced interesting results they have nevertheless failed, in that no definite conclusions as to the function of any one nucleus or region have been demonstrated. At best, movements of the head, eyes and body and various movements of the limbs more or less associated have been observed. What effect these combined activities would produce in a normal free animal could only be guessed at.

As an illustration of the difficulties encountered in attempting to determine what effect these combined activities would have on the animal, the argument from the paper of Ingram, Ranson and their associates may be cited. After mentioning that the response obtained by stimulating the mesencephalic tegmentum usually conforms to a definite stereotyped pattern—the head and trunk curved to the side stimulated with flexion of the foreleg; on the opposite side the foreleg extended, while the movements in the hindlegs varied between flexion and extension—they mentioned that it is difficult to think of any useful purpose which the association of such movements could subserve in the normal animal. They considered that the only comparison to be found is in the locomotor efforts of Amblystoma larvae when removed from the water. Furthermore, the question is seriously considered whether the mesen-

12. Ingram, W. R.; Ranson, S. W.; Hannett, F. I.; Zeiss, F. R., and Terwilliger, E. H.: Results of Stimulation of the Tegmentum with the Horsley-Clarke Stereotaxic Apparatus, Arch. Neurol. & Psychiat. **28**:513 (Sept.) 1932.

cephalic tegmentum retains in its adult arrangement a phylogenetically old pattern from which by direct stimulation an ancient type of reaction not normally evoked in postnatal life may be elicited.

Any method of investigation which produces reactions which can be interpreted only by one who has a profound knowledge of the activities of animals in the lower brackets of the phylogenetic scale could never be of much practical value. Fortunately these responses can be more easily explained.

In looking for the reason why the stimulation of localized regions has failed to produce definite reactions that were clearly understandable, two serious defects in the application of the method were found, viz., the anesthetic and the fixation of the animal. The anesthetic must interfere with the effect of the stimulation, and the fact that the animal is under restraint naturally limits its activities.

After carefully examining these difficulties there appeared to be only one way that might definitely show normal function, and that was to stimulate, without an anesthetic, an intact animal that was quite unhindered in its movements.

Recently such a method has been developed, and it is now possible actually to see the reactions that are produced in a normal animal, sitting or lying quietly on the floor or moving freely about, when some particular region is stimulated.

METHOD

The success of the method depends on the correct insertion and fixation of a bipolar electrode into the particular region to be examined. The electrode is composed of two iridioplatinum wires fastened to terminals in a vulcanite base and insulated in glass tubes. The base fits into a metal cup which is screwed into the bone. The cup directs the electrode while it is being inserted, and by means of a bayonet joint attachment holds it firmly. A cylinder with a flange screws over this to keep the tissues from the electrode, and about this the skin and muscles can be firmly closed. Finally a cap is screwed over the cup to protect the terminals. The size of the electrode is 1.5 mm. in diameter, the length varying according to the depth from the surface of the bone of the structure to be investigated. The trephine is 5 mm. in diameter. The brain is not exposed, the dura being only punctured. The electrode and the manner of its insertion are illustrated in figures 1 and 2.

The Operation.—The animal is anesthetized and the head fixed in the stereotaxic instrument. Measurements of the head are then taken, the indicator is adjusted, and the position of the structure to be examined is marked. The skull is then trephined at the proper point, and the cup of the electrode unit screwed into the bone. The bipolar electrode is next inserted; the flange is screwed on and then the cap. The skin and muscle are closed tightly about the unit, and the field of operation is dusted and bandaged.

Examination.—On the following day, when the animal has completely recovered from the effects of the operation and the anesthetic, the bandages are removed and the general condition investigated. In an experiment of this kind, in which the

animal is entirely unrestrained, the success of the examination depends on its cooperation. By gentle treatment—washing the face, rubbing the head and throat, pulling the ears and stroking the back—the ordinary cat will respond normally by purring. And it is of interest to note that the presence of the electrodes screwed into the skull does not cause any pain or uneasiness. In no instance has an

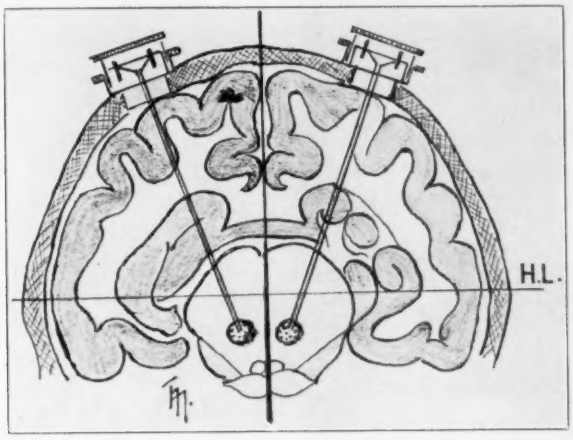

Fig. 1.—The electrode unit, with the metal cup screwed into the bone, and the bipolar electrodes inserted into the red nuclei. As the surface of the skull is curved and the engaging base of the metal cup is flat, considerable difficulty is met with in maintaining the correct angle. This explains why the right electrode in the first experiment crossed the median line to enter the left red nucleus. *H.L.* indicates the horizontal line.

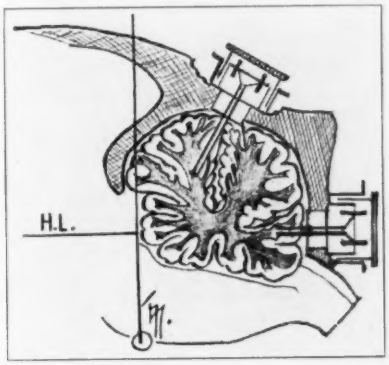

Fig. 2.—Electrodes in the anterior and posterior vermis.

effort been made to scratch at them. Even during the stimulation there is no evidence of any local distress. Occasionally an outlaw will be met with, any attempt at handling being resisted by biting and scratching. It is impossible to examine such an animal.

With the animal in a friendly mood it is put through a number of simple tests. The gait and righting reflexes are observed, and also its ability to jump from a

table and walk backward on the hind legs when it is supported by the shoulders. With few exceptions the reactions are normal, and the cat sits or lies quietly on the floor, frequently purring contentedly and waiting patiently for the next event, which consists of attaching the plug from the faradic battery and testing the reactions.

The present preliminary report deals with the results obtained from three different regions: the red nucleus, the anterior region of the thalamus and the cerebellum. As the reactions in each experiment are distinctly different, it will be obvious that they must arise locally, and as the weakest current that can give a response is used there can be no question of spread. The strength of the current is indicated by the sensation produced by the points of the electrode when applied to the tip of the tongue. With the secondary coil at 17 cm. a slight tingling is felt; at 13 cm., the sensation is painful; contraction begins at 12 cm., and is very marked at 8 cm.

THE RED NUCLEUS

The red nucleus, which is always interesting on account of its position in the cerebellar arc and of the function of which practically nothing is known, offered an important test. In my previous stimulating experiments the only responses obtained were movements of the eyes from the third nerve (head and limbs negative). Destructive lesions in the posterior regions of the nuclei with bilateral and symmetrical degenerations of the rubrospinal tracts had also caused no disturbance, though a lesion involving the nucleus parvocellularis on the left side, with degeneration in the crossed rubrocervical tract, resulted in a loss of the opposite righting reflex and a rotation of the animal in circles to the right, i. e., toward the healthy side. These significant symptoms, suggesting the influence of the right nucleus, intrigued me to another trial. In the first experiment only one electrode was introduced, as it was feared that the screwing of the metal cap into the bone and the presence of the electrode in the brain might cause too much disturbance.

EXPERIMENT 1.—*Cat 395.*—Jan. 23, 1933. Red nucleus, left side.
Operation: Electrode introduced.
January 24: Examination. Animal responded normally to tests.

Stimulation

Strength of Current:	Reactions:
17 cm.:	Head to left, extended upward and backward; chin pointed left.
16.5 cm.:	Same but stronger reaction, with raising of right shoulder and lifting of right foreleg.
	During stimulation cat had remained in upright sitting posture.
	At rest a normal lying position was assumed, the head being in the median line but slightly rotated, right ear downward.
	January 25: Movies taken.
15 cm.:	Head rotated to left until chin pointed over back.
14 cm.:	Cat rotated in 2 foot circle to left, pivoting on hindlegs.
	The character of these reactions is shown in some strips from the motion pictures (fig. 3). The photograph of the section (fig. 4) shows that although the electrode was inserted from the right side it was in contact with the dorsal part of the left red nucleus.

Summary.—This experiment demonstrates that when the left nucleus is stimulated, the head and body turn to the left, and the animal rotates in a small circle to the left.

EXPERIMENT 2.—*Cat 398.*—Feb. 3, 1933. Red nucleus. Operation: Electrodes introduced from right and left sides so that the reactions might be compared.

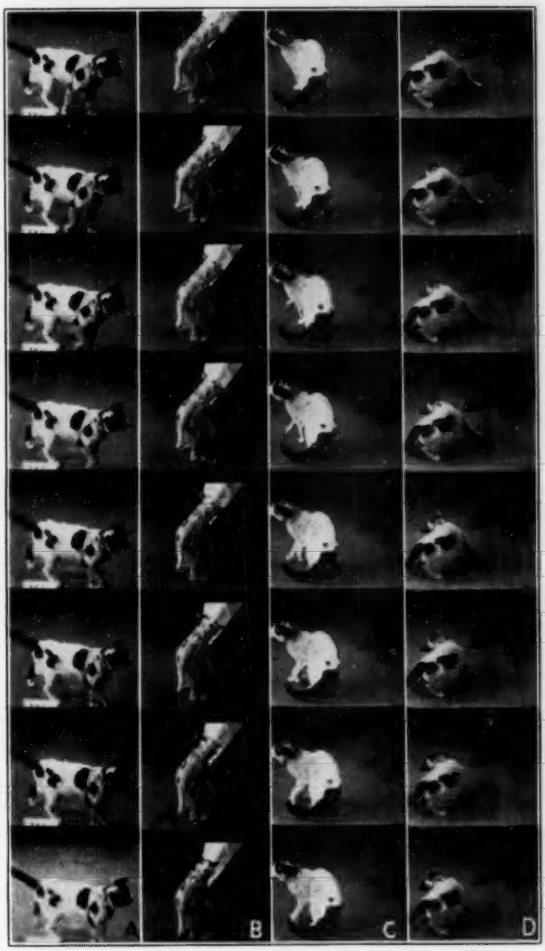

Fig.—3.—Reaction in cat 395, with one electrode in the left red nucleus. *A* shows the cat walking about normally, the head slightly rotated to the left; *B*, head upward, backward and to the left; the right shoulder and forepaw are raised; *C* and *D*, the head slightly rotated to the left, the left ear down. The head and body are flexed to the left, rotating in a small circle to the left.

February 4: Conditions satisfactory. Reactions normal.

Stimulation of right side

Strength of Current:	Reactions:
16 cm.:	Head and body to left, rotated to left with slow steady movement.

Stimulation of left side

Strength of Current:	Reactions:
16 to 11 cm.:	No response.
10 cm.:	Head and shoulders flexed, nose to floor. Rotated in rapid circles to left.

Stimulation of both right and left sides

14 cm.:	Head and body turned to left. Rotated to left, pivoting on hindlegs.

Comment.—These results were distinctly puzzling as similar but opposite reactions had been looked for. Each side gave the same reaction. But the explanation was clear when the brain had been removed and the section examined. It was then seen that the right electrode had crossed the median line to enter the left red

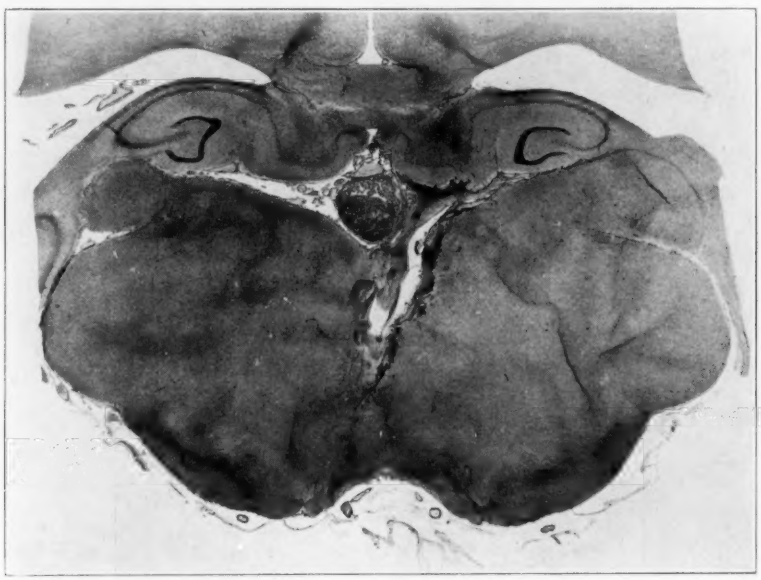

Fig. 4.—Section from cat 395, showing the path of the electrode, which was inserted from the right side, crossing the midline to enter the left red nucleus.

nucleus, in its dorsal and median region. The left electrode was also in the lateral part of the left red nucleus, so that both electrodes were in contact with different parts of the left red nucleus.

Summary.—Again the left red nucleus turned the head and body to the left, and the animal rotated in circles to the left.

EXPERIMENT 3.—*Cat 401.*—Feb. 16, 1933. Red nucleus, left side.

Operation: Electrode inserted.

February 17: Condition satisfactory. Reactions normal. Stimulation.

Strength of Current:	Reactions:
19 cm.:	Crouched, turned left and ran forward.
18 cm.:	Jumped up, both forepaws in the air; ran forward.
17 cm.:	Turned to left and ran forward.
16 cm.:	Turned to left, ran to left and forward rapidly. As soon as the current was turned off, stood perfectly still.

Summary.—Again the cat turned to the left, but in this instance it ran forward. In the photograph of the section (fig. 5) the point of the electrode is in the left red nucleus.

TABLE 1.—*Summary of Results of Studies on the Red Nucleus*

	Method of Investigation	Reactions
1926.	Stimulation (with anesthetic)	No response
1927.	Lesion in left nucleus, anterior region	Under the unopposed activity of the right nucleus; The head and trunk are curved to the right The animal rotates in circles to the right, pivoting on its hindlegs
1933.	Stimulation, left nucleus (without anesthetic)	Head and trunk curved to the left; animal rotates in circles to the left, pivoting on hindlegs

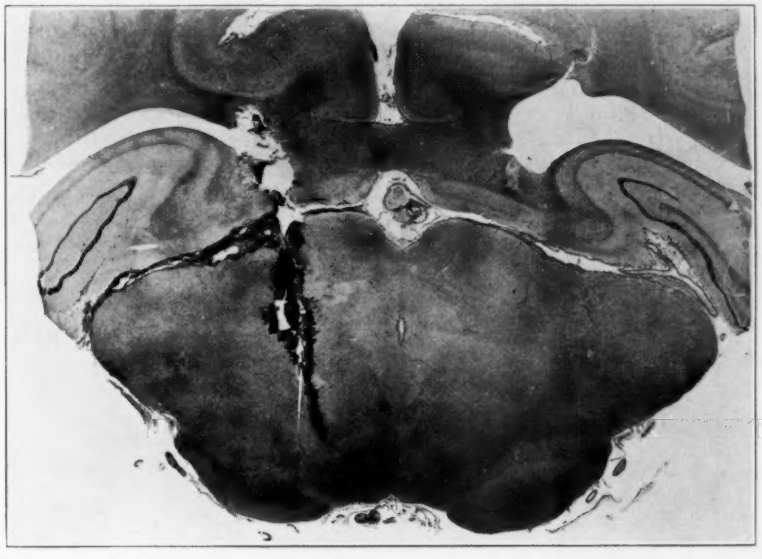

Fig. 5.—Section from cat 401. The electrode entered from the left side, and the point is directly in the left red nucleus.

It is unfortunate that in these three experiments on the red nucleus in intact animals the left nucleus was the only one which was successfully stimulated. But as the reactions in each case were practically the same, i. e., flexing the head and body to the same side as the nucleus and rotating in the same direction, it seems reasonable to conclude that the nucleus is concerned in these movements. Considered more particularly, these responses showed a curving of the head and trunk to the side stimulated, flexion of the foreleg on the same side and extension of the foreleg on the opposite side, while the hindlimbs showed movements

between flexion and extension. These are the reactions which another observer could not interpret as serving any useful purpose in the normal animal.

THE THALAMUS

As it has been claimed by other observers that the region anterior to the red nucleus gives practically the same reactions as the neighborhood of the red nucleus, it was decided to investigate by this method. The following experiment is reported to show that there is a distinct difference.

EXPERIMENT 4.—*Cat 404.*—March 1, 1933. Thalamus, anterior ventral region.
Operation: Electrodes inserted right and left sides.
March 2: Condition satisfactory, reactions normal.

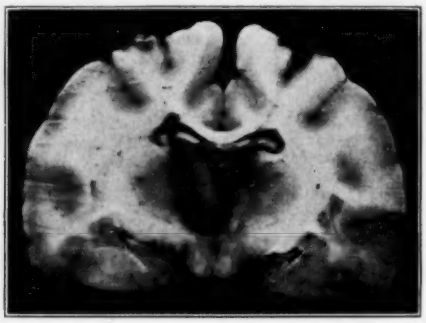

Fig. 6.—Section from cat 404. The electrodes were inserted into the anterior region of the thalamus, the ventral part being stimulated.

Stimulation of right side

Strength of Current: — Reactions:

17-15 cm.: No response.

13 cm.: Both pupils widely dilated; hair on back and tail stood up; animal cried softly. No movement in extremities. Half a minute later cat was lying quietly on the floor (fig. 7 *B*).

12 cm.: Eyes and pupils widely dilated. Head held low and turned to left. Whole body directed to left in a circular movement. Hair on back and tail strongly erect. Animal gave the impression of seeing something on left side of which it was afraid and backed away from it sideways (fig. 7 *A*).

Stimulation of left side

15 cm.: Head rotated downward to left; right paw raised (fig. 7 *C*).

16 cm.: Eyes opened widely; pupils dilated; slight movement of head to right. During stimulation animal stood in one place.

14 cm.: Head and shoulders rotated so far to left that cat was pulled completely over on to the left side.

Stimulation of both sides together

16 cm.: Eyes widely opened; pupils dilated; head to left; hair up on back and tail (figs. 6 and 7 *D*).

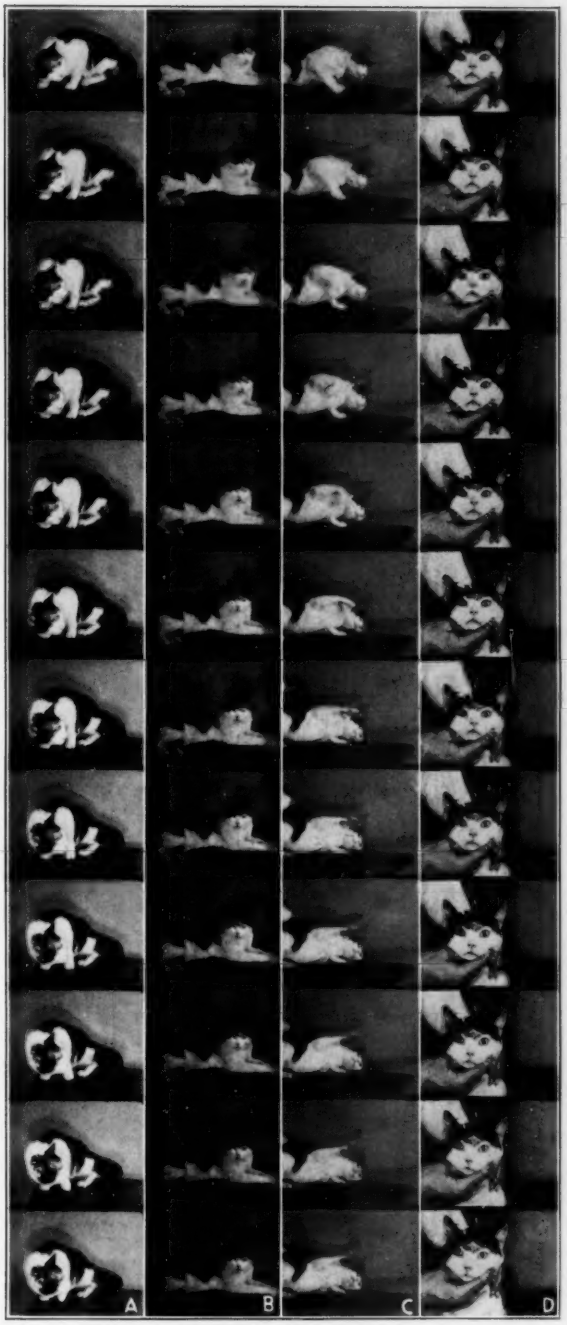

Fig. 7.—Experiment on cat 404. In *A* the reaction suggests fear. The head is down, the eyes are widely opened, and the pupils are dilated. A crouching position is assumed, the hair on the back and tail being erect. The cat appears to see something from which it is backing away. In *B* the cat is at rest between stimulations. The position is very natural. There is no sign of any discomfort. *C* was taken after stimulation of the left side. The head and shoulders were rotated so far that the cat rolled over. The forelegs are abducted and extended. *D* shows the extreme opening of the eyes and dilatation of the pupils when both sides are stimulated.

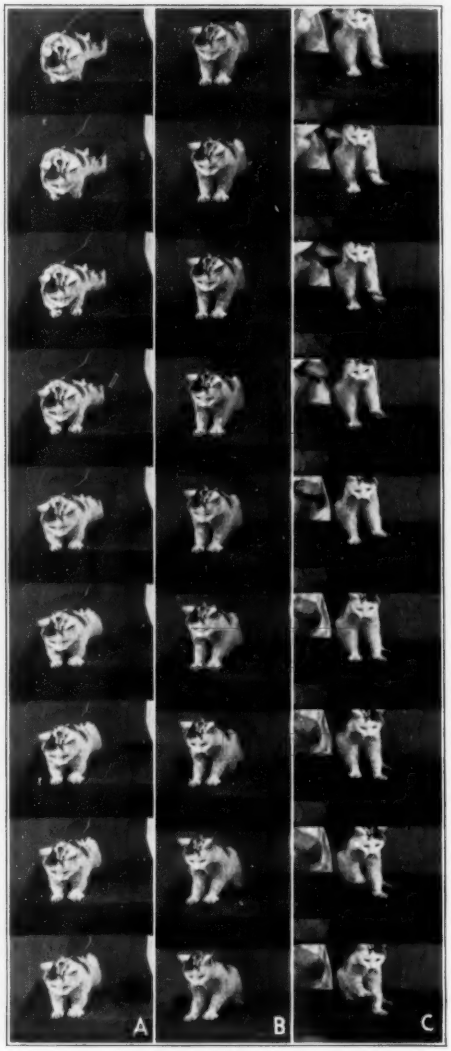

Figure 8

Figure 9

Fig. 8.—Experiment on cat 412. Stimulation of the anterior vermis. The animal is raised to a sitting posture through the contraction of the posterior muscles of the neck. After reaching this position the right and left forelegs, rigidly extended, are raised alternately.

Fig. 9.—Experiment on cat 412. Stimulation of the posterior vermis. The head is held low, being pressed against the table, owing to the contraction of the anterior muscles of the neck.

THE CEREBELLUM

My previous stimulating experiments [13] on the anesthetized animal had shown that the anterior vermis influenced the contraction of the posterior muscles of the neck, pulling the head up and back, extending the forelegs and flexing the hindlegs, reactions that would be called into play whenever forward balance was threatened. The posterior vermis had also been shown to be related to the anterior muscles of the neck, pulling the head down, flexing the forelimbs and extending the hindlimbs. It was considered that these two lobes with antagonistic reactions were responsible for the maintenance of forward and backward equilibrium. Therefore if the anterior lobe was destroyed the posterior muscles of the neck would be put out of action; the posterior lobe would function without opposition, and the animal would fall forward. Following a lesion in the anterior vermis, forward balance was lost, and

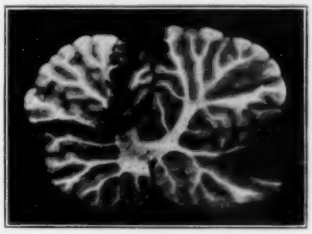

Fig. 10.—Experiment on cat 412, showing the position of the electrodes in the anterior and posterior vermis. For reactions see text.

the destruction of the posterior vermis resulted in a loss of backward balance. Here was another region of particular interest to investigate by this method.

EXPERIMENT 5.—*Cat 412.*—April 3, 1933. Cerebellum. Operation: Electrodes inserted into the anterior and posterior vermis.

April 4: Condition satisfactory, reactions normal.

Strength of Current:	Reactions:
	Stimulation of posterior vermis
18 cm.:	Head to floor, turned to left; ran forward in crouching position.
	Stimulation of anterior vermis
18 cm.:	Head moved slightly upward. Before next stimulation the cat was lying down on right side with limbs outstretched, head on floor.
16 cm.:	Righted itself; raised head and shoulders; stood up; ran forward.
11 cm.:	Head raised from lateral to ventral position; shoulders raised; head drawn back; forelegs extended; hindlegs flexed.

13. Mussen, A. T.; The Cerebellum: A New Classification of the Lobes Based on Their Reactions to Stimulation, Arch. Neurol. & Psychiat. **23**:411 (March) 1930.

April 5: Movies taken.

Strength of Current:	Reactions:
	Stimulation of anterior vermis
22 cm.:	Animal raised to sitting posture, head to left, right paw raised.
22 cm.:	repeated: Head raised; forelegs extended, pushing body upward.
21 cm.:	Head and shoulders raised; forelegs extended rigidly, performed a pawing movement, right and left alternately (fig. 8).
	Stimulation of posterior vermis
20 cm.	Head kept lowered, no other response (fig. 9).

Comment.—The position of the electrode in the anterior lobe of the vermis is well shown in figure 10. In the posterior vermis there was considerable damage, which would account for the absence of reactions.

TABLE 2.—*Summary of Results of Studies on the Cerebellum*

Method	Anterior Vermis Reaction	Posterior Vermis Reaction
Stimulation with anesthetic (1930)	Posterior muscles of neck contracted; head drawn up and back; forelegs extended; hindlegs flexed; forward equilibrium controlled	Anterior muscles of neck contracted; head drawn down and forward; forelegs flexed; hindlegs extended; backward equilibrium controlled
Lesion (1931)	Posterior muscles of neck did not respond to disturbed equilibrium; anterior muscles of neck acted unopposed; animal fell forward	Anterior muscles of neck did not respond to disturbed equilibrium; posterior muscles of neck acted unopposed; animal fell backward
Stimulation without anesthetic (1933)	Posterior muscles of neck contracted; head drawn up and back; forelegs extended; hindlegs flexed	Anterior muscles of neck contracted; head drawn down and forward; forelegs flexed

SUMMARY AND CONCLUSIONS

The question arising from these investigations is this: If similar reactions are obtained from the same region by means of different methods, is one justified in concluding that the responses represent, in part at least, the physiologic activity of that region? If the answer is in the affirmative, as it appears it should be, then two distinct physiologic reactions have been demonstrated:

1. In the cerebellum the synergic activity which regulates forward and backward balance is located in the anterior lobe of the vermis, and in the pyramid of the posterior lobe.

2. The red nucleus is concerned with the flexion of the head and body and with rotation movements toward the side of the nucleus.

This means that when the red nucleus is stimulated impulses are set up which are responsible for the following group of activities: turning and lowering the head; rotation of the head on the neck; conjugate deviation of the eyes; flexion of the trunk; alternate flexion and exten-

sion of the limbs; backward and lateral pushing movements in the forelegs, with slight shifting movements in the hindlegs which enable the animal to rotate in a backward circle, pivoting on its hindlegs, and a constantly shifting equilibrium so that at all times a normal balance is maintained.

If the simple stimulation of a nucleus (with a current so weak that the possibility of spread can be excluded) will produce such a complex group of coordinated activities, it obviously suggests that the nucleus is the responsible center. Considered from this point of view, its position is suggestive for it lies in the midst of the nuclei of the brain stem in many of which the afferent tracts terminate—thalami, geniculates, colliculi and lenticular nuclei; it is also in close relation with the posterior longitudinal fasciculus, the pyramidal tracts and the central tegmental bundles. It is thus easily accessible to every influence.

One may therefore postulate that the red nuclei are the central stations for the reception of information from all sources, and from which commands are sent forth which regulate and harmonize every activity so that the animal is able to respond to stimuli with such extraordinarily complicated yet perfectly coordinated reactions.

But these few experiments are, of course, not to be considered as final. The purpose of this report was to demonstrate the possibilities of a new method. Even though the results have more than justified my expectations, there is every reason to believe that with improved and smaller electrodes and a better technic it will be possible to insert six or eight electrodes and, by hooking these to a keyboard, to make the animal go through a variety of movements. Some of these cats have already been kept for three weeks. With particular care in the sterilization of the electrodes it should be possible to keep them under observation much longer, for the brain is not exposed and the incision in the skin and muscle is very slight.

DISCUSSION

Dr. J. G. Dusser de Barenne, New Haven, Conn.: With regard to the last remark Dr. Mussen made, of course, in experiments on stimulation in the interior of the central nervous system one often stimulates afferent and efferent systems. Now in this instance, that of the cerebellum, one may stimulate fibers going up to the cortex and fibers going out from the nucleus dentatus. So the difficulty is to find out exactly the stimulation of which systems produces the effects. How did Dr. Mussen solve this difficulty?

Dr. Joshua Rosett, New York: Has Dr. Mussen thought of an explanation that would reconcile the results of his work, which we have seen so beautifully demonstrated, with the work of other investigators in the same field? Dr. Mussen's experiments show that movement of certain parts of the body can be produced by stimulation of definite parts of the cerebellum. In the hands of Dr. Mussen the cerebellum assumes a function which is very much like that of the precentral convolution of the cerebrum. His findings, therefore, differ greatly from those of other investigators who have shown that stimulation of the cerebellar cortex results in an abatement of decerebrate rigidity. In terms of normal physiology, the latter

fact implies that the normal activity of the cerebellar cortex brings about the diminution of tonus in certain groups of muscles contracted in postural reflexes which is necessary for the production of movement. In brief, Dr. Mussen's work tends to show that the normal activity of the cerebellum is the production of movement, while the work of other investigators shows that the normal function of that organ is abolition of the posture which immediately precedes movement. Since Dr. Mussen's work tends to negate the results of the work which preceded his own, it is incumbent on him to show the cause of the discrepancy.

DR. COLIN K. RUSSEL, Montreal, Canada: Have you been able to repeat the same pattern of movement in different animals on stimulation of the same nucleus?

DR. AUBREY T. MUSSEN, Baltimore: My previous stimulating experiments have shown that the cortical reactions of the various lobes of the cerebellum have been entirely different from each other. The nuclei have not been examined. But as the nuclei receive afferent fibers from many lobes, they would probably show some results that are simple and others that are of a more complex nature.

In my cerebellar experiments, with the head of the animal fixed in the Horsley-Clarke instrument, on stimulating the anterior vermis the head was drawn upward and backward, and the forelegs were extended. Stimulation of the posterior vermis produced the opposite reaction. I argued from this that if the anterior vermis did influence the activity of the posterior muscles of the neck, then a destruction of the anterior vermis would interfere with the response of these muscles, and the anterior muscles of the neck acting without opposition would pull the head forward and downward, lessening the extensor tone in the forelegs, and forward balance would be lost. If the posterior vermis was destroyed, the normal response in the anterior muscles of the neck to disturbed equilibrium would be interfered with, and the posterior muscles of the neck acting without opposition would pull the head upward and backward, extending the forelegs and flexing the hindlegs, and the animal would fall over backward. These observations were proved to be correct.

Thus by three different methods—(1) stimulation with the Horsley-Clarke instrument, the animal being anesthetized and under restraint, (2) destructive lesions, the animals being examined through subsequent weeks and (3) stimulation by the new method of fixed electrodes, the animal being unanesthetized and quite free—the influence of the anterior and posterior vermis has been demonstrated. The results show that the responses are similar (i. e., that the reactions due to the stimulation of the anterior vermis are the same as those produced by a lesion of the posterior vermis, viz., loss of backward balance), that the lobes have antagonistic reactions, and are therefore complementary to each other, and that on them in the first analysis (because later equilibrium is reestablished) the regulation of forward and backward balance depends.

In regard to Dr. Rosett's remark, it is difficult to compare reactions obtained in this way on an intact animal with the effects produced by other methods under entirely different conditions. In this instance the animal turned in circles to the left when the left red nucleus was excited. And in a previous experiment the animal turned in circles to the right, that is, toward the normal right red nucleus, when the left had been destroyed. When the same reactions can be obtained by two such entirely different methods, it seems reasonable to consider that the nucleus under investigation is responsible.

In reply to Dr. Russel, about half a dozen experiments on the red nucleus have been tried. But the various reactions here described are not to be considered as final. They have been shown only to illustrate the practical results that may be obtained by this new method of investigation.

DISSOCIATION OF THE HOMOLOGOUS MUSCLE FUNCTION IN STUTTERING

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IOWA CITY

With the exception of certain viscera, such as the heart and the liver, all corresponding structures in the body are repeated and reversed symmetrically, i. e., they express the condition of antitropy. Although any two homologous structures, such as the feet, the hands and the cerebral hemispheres, are of comparable constitution, they differ structurally in that one is the mirrored counterpart of the other. Orton [1] has held that this antitropic condition exists for function as well as for structure. For example, innervation of certain muscles of the left hand results in an activity which is exactly opposite, in respect to the midline, to that which results from the innervation of corresponding muscles of the right hand. This principle is recognized in the assumption that mirror writing with the left hand is the normal sinistral expression. In the coarser movements of the primary muscles, e. g., those of the extremities, antitropy does not appear to play such a large part. This may be due largely to the separatistic aspect of the movements involved. However, the muscles of speech on either side of the midline present a situation comparable to that which would exist if the two arms or the two legs were required to react always in unison as single structures. The possibilities for disturbance of function may be viewed as increasing when one considers the need for nice adjustments of the muscles concerned in the ambidextrous functioning of the midline muscles of the speech mechanism.

The peripheral speech mechanism is made up of several organs functioning as a unit, over which innervations from both cerebral hemispheres have a synarchic control. So far as this joint government is harmonious the central prerequisites for normal speech have been fulfilled. However, this unusual anatomic situation offers possibilities for abnormality of function, since dual control of a single mechanism might permit of a disorganizing, ambivalent leadership. It is in relation to such possibilities that I have conceived the present study.

The muscles of speech chosen for action current study were the masseter muscles. Their selection was determined primarily by the fact

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From the Psychopathic Hospital.

1. Orton, S. T.: "Word-Blindness" in School Children, Arch. Neurol. & Psychiat. **14**:581 (Nov.) 1925.

that they are readily accessible for the accurate placement of electrodes on them without appreciable interference with the production of speech. Furthermore, I have found that these muscles are active almost continuously during speech, thereby assuring neuromuscular activity for study during essentially all attempts at speech.

APPARATUS AND METHOD

The apparatus used for the tests has been described by Travis and Dorsey.[2] Briefly, it consisted of a Westinghouse oscillograph, a General Radio type 377-B low frequency oscillator and two resistance-coupled amplifiers. The two oscillograph elements employed with the amplifiers were adjusted to the identical sensitivity of 0.045 inch deflection per milliampere. The amplifiers were perfectly matched and noninterfering. The amplifying recording units had flat frequency-deflection curves of between 90 and 900 complete cycles per second for a constant input voltage. The electrodes were made of thin brass strips, 40 mm. long and 15 mm. wide, covered with canton flannel which was saturated with concentrated saline solution. One pair of electrodes was placed over one masseter muscle and the other pair over the other masseter muscle. The electrodes of each pair were placed approximately 1 cm. apart. Great care was exercised to see that the two pairs of electrodes were placed on exactly homologous areas of the two muscles. For making the majority of the records the oscillator activating an oscillograph element was adjusted to provide time values of 0.002 second. All recording was done on Eastman, no. 1, 35 mm., sensitized paper.

The action currents were recorded simultaneously from the two masseter muscles during speech in easy, unemotional, conversational situations. The subjects taking the test discussed current topics of the day, answered questions and entered into conversation with the experimenter. Recording was continued until it was thought that an adequate sample of the subject's speech had been obtained.

EXPERIMENTAL RESULTS

Action current records were secured from twenty-four adult stutterers and an equal number of adults who speak normally. During the apparently normal speech of twenty-two of the normal speakers the action currents from the two masseter muscles were practically identical in regard to instant of appearance, frequency, intensity, duration and general patterning (fig. 1). Furthermore, the action currents from both masseter muscles in normal speakers generally appeared continuously during speaking, presenting variations in intensity with variations in the amount of activity of the muscles. During some of the apparently normal speech of two of the normal speakers the action currents from one masseter muscle (the right in one case and the left in the other) were larger than those from the other masseter muscle.

2. Travis, L. E., and Dorsey, J. M.: Action Current Studies of Simultaneously Active Disparate Fields of the Central Nervous System of the Rat, Arch. Neurol. & Psychiat. **28**:331 (Aug.) 1932.

During the stuttering of eighteen of the stutterers the action currents from one masseter muscle were strikingly different from those from the other masseter muscle. The action currents from one side would be large, while those from the other side would be small (fig. 2 *A*): those from one side would appear at a rate of from ten to forty volleys per second while those from the other side would be absent or would appear in much smaller, irregular volleys (fig. 2 *B*); the volleys from one side would appear out of time with those from the other side, both earlier and later (fig. 2 *C*); the action currents from one side

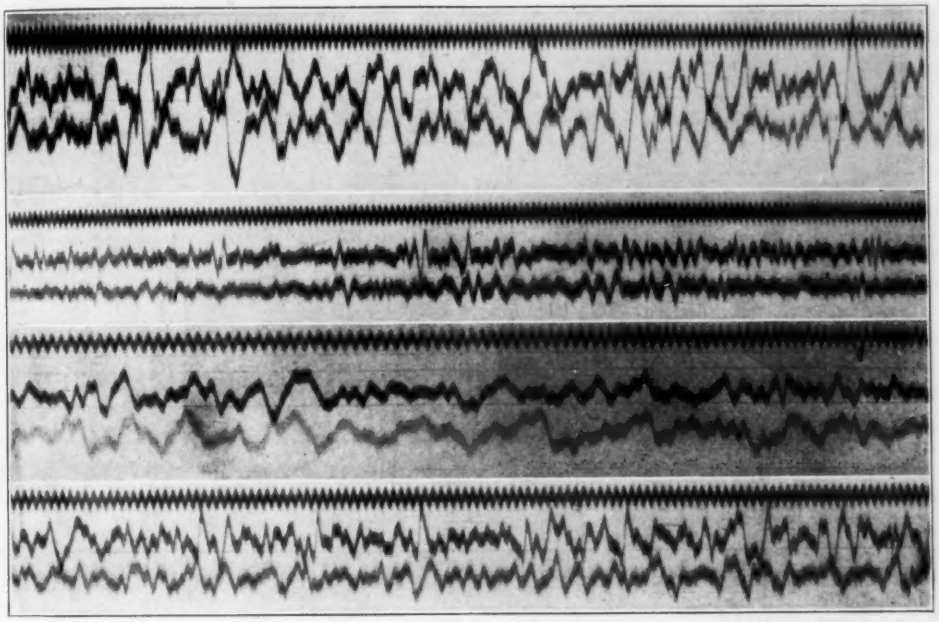

Fig. 1.—Action current records from the two masseter muscles of normal speakers during normal speech. In each strip, as in figure 2, reading from the top downward, the first line is the time line, the second is an action current pattern from the left masseter muscle and the third is an action current pattern from the right masseter muscle. In these records the time is in 0.002 second.

would be of much greater frequency, and both larger (fig. 2 *D*) and smaller (fig. 2 *E*) than those from the other side; those from one side would give a strikingly different pattern from that shown by those from the other side (fig. 2 *F*); and those from one side would present the periodic appearance of a single large action current wave (sixteen times per second) while those from the other side would be uniformly small (fig. 2 *G*). During the free speech of all, and during the stuttering of six, the action currents from one masseter muscle of the stutterers

were not strikingly different from those from the other masseter muscle, nor were they significantly dissimilar in any other respect to the action currents made by normal speakers.

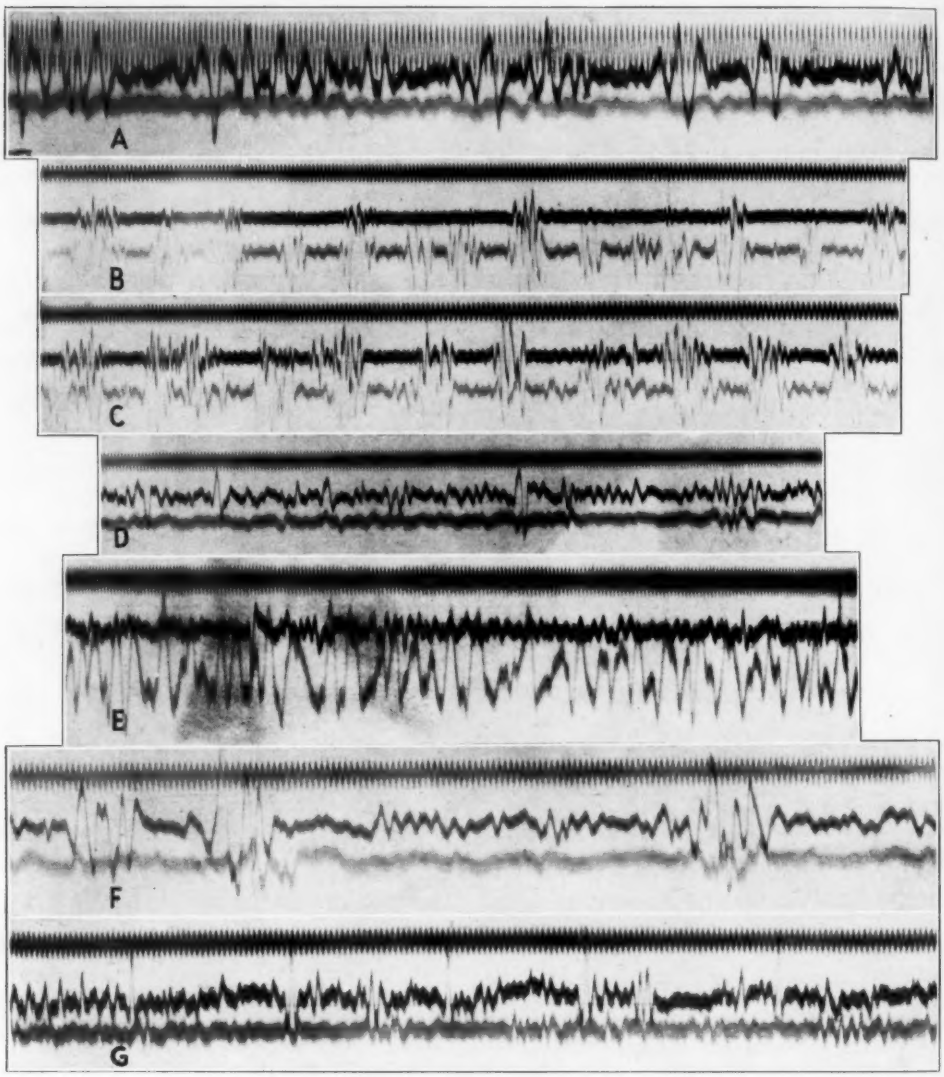

Fig. 2.—Action current records from stutterers during stuttering. The time in *A*, *D*, *E* and *F* is in 0.001 second and in *B*, *C*, and *G* it is in 0.002 second.

Considering the intensity of the action current alone, only two stutterers gave consistently larger action currents in one muscle than in the other (left in both cases) during stuttering. All the other

stutterers gave larger action currents first in one muscle and then in the other during stuttering. Generally, throughout the stutterer's record there were relatively short intervals of time during which the action currents of one side were approximately equal in size to those of the other side. When this did occur the action currents varied from the normal in presenting periodic and aperiodic volleys, periodic and aperiodic large single waves, and differences in form and in frequency between the sides.

To check the results secured during stuttering, action currents were recorded from several of the stutterers and the normal speakers during their attempts to produce voluntarily as many stuttering symptoms as possible. In successful imitative stuttering there was not a single instance of either a normal speaker or a stutterer voluntarily producing abnormalities in the action current similar to those obtained during true stuttering. A number of the stutterers were never able, and none of them was always able, to maintain voluntary control over the speech apparatus in imitative stuttering; i. e., their voluntary efforts, sooner or later, were interrupted or replaced by true stuttering spasms. The shift from voluntary to real stuttering was easily discernible in the action current records. These results indicate, it may be added, that basically neither the stutterer nor the normal speaker can voluntarily produce true stuttering.

COMMENT

The general finding of the study is that from the standpoint of action current records the two masseter muscles function similarly, if not identically, during normal speech, while they function dissimilarly, if not antagonistically, during stuttering. Assuming that the action of the masseter muscles typifies the action of other muscles of speech, one sees here the two sides of the peripheral speech mechanism functioning as a unit in normal speech. Inasmuch as the nerve impulse initiates muscular contraction and the action currents result from both, one may say that during the act of normal speech the two halves of the speech mechanism receive similar innervation and are equally capable of responding to that innervation.

A complete act of speech is a widespread response of the organism, which employs several levels of the central nervous system in its execution. It requires the highest type of nervous integration. To make this integration possible such factors as dominance of higher over lower levels and unification of control on the part of the two cerebral hemispheres probably play an important rôle. It has been amply demonstrated both clinically and experimentally that the first factor enters into the realization of nervous integration. A study bearing on the second factor has been reported by Travis and Dorsey.[2] They found that

during voluntary activity of the rat, synchronization and isomorphism of the two action-current patterns from the cerebral hemispheres ranged from a small amount in the two auditory fields to a great amount in the two motor fields. This means that as the final common motor pathways of the two hemispheres are approached, the right and the left motor frequencies in some way coalesce to form that perfect synarchy which is indispensable to singleness of purpose. Although the action currents from the two masseter muscles were not synchronous (and one could not expect to find them so in view of the complexity and degree of separation of the two muscle masses), the two patterns were almost identical with regard to instant of appearance, frequency, intensity, duration and general form of the action current waves. This implies that the two muscles (the two sides of the speech mechanism) were receiving essentially the same innervation in spite of the bilateral origin of their nerve supply and were equally capable of responding to that innervation.

During stuttering the two masseter muscles gave strikingly dissimilar action current patterns. It is certain that either the muscles were not receiving the same or similar innervation or they were not capable of responding equally to such innervation.

I do not know of physiologic or biochemical evidence to support the second possibility, which implies that in the stutterer a given muscle of a pair may be significantly different from its mate in response characteristics. Since the two muscles sometimes respond differently and sometimes similarly, the findings may not be viewed as manifestations of a generalized muscular inadequacy which would obtain on any known biochemical basis. Thus it would appear that the difference in action current pictures from the two sides was of neurologic origin. The level of origin of the dissimilarity of nervous activity in the two sides of the nervous system is unknown. It could have been the motor nuclei of the trigeminal nerve or any of the levels making connections with these nuclei, such as Deiters' nuclei, the red nuclei, the corpora striata and the motor cortices of the cerebral hemispheres.

Students of biology recognize the fact that characteristics of early phylogenetic origin are generally modified less easily than are later acquisitions. It is very likely that this rule holds for the neural levels. If so, one would expect the highest levels to present the greatest susceptibility to hereditary factors and environmental influences, and there is good evidence that this is true. It follows that the cerebral hemispheres would be most subject to dysfunction. Then there is some justification for assigning the origin of the dissimilarity of innervation of the speech muscles during stuttering to the cortex cerebri. Here the possibilities for change are much greater than in the subordinated

levels, which are fundamentally more stable. Further, since speech is such a completely overlaid function and depends to a great degree on the highest integration of the movements of the individual parts of the speech mechanism, one might think of the breakdown as occurring at that level (cerebral) which has the most to do with integration.

Noteworthy exceptions to the general findings of this study were that during apparently normal speech two of the normal speakers gave dissimilar action current patterns from the two masseter muscles, and that during stuttering six of the stutterers gave similar patterns from the two muscles. It is possible that unobserved stuttering occurred during the speech of the two normal speakers. This seems plausible in view of the following facts: 1. Normal speakers sometimes do stutter (two others among our normal subjects actually did stutter when talking during the experimental situation). 2. One of the two normal subjects was a noticeably uncertain, hesitant speaker. There are at least three possible explanations of the exceptions among the stutterers: 1. The six stutterers did not stutter while the records were being taken. 2. The stuttering did not express itself in the masseter muscles. 3. The stuttering did not express itself in any detectable neurophysiologic disturbances. All of these six stutterers had extremely mild cases, and there was considerable doubt as to whether or not they stuttered when the action current records were being obtained. Studies of the vocal and breathing disturbances of stutterers show that certain parts of the speech mechanism may be functioning normally while other parts are functioning abnormally. Thus it might have been that in these six stutterers structures other than the masseter muscles were affected in the stuttering.

SUMMARY

Action currents were recorded simultaneously from the two masseter muscles during the stuttering and during the free speech of both the stutterer and the normal speaker. Twenty-four adult stutterers and an equal number of normal speakers served as subjects.

In general, during normal speech the action currents from the two masseter muscles were identical, while during stuttering those from one masseter muscle were strikingly different from those from the other. These findings indicated a unified control by the central nervous system of the two sides of the speech mechanism during normal speech and a lack of such control during stuttering.

Clinical Notes

SO-CALLED FUNCTIONAL HYPOPITUITARISM

Pathologic Findings and Report of a Case

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Marie's [1] description of pituitary tumor with acromegaly and Fröhlich's [2] description of pituitary tumor associated with adiposity, dwarfism and genital dystrophy may well be said to have opened the modern era in our present knowledge of the pituitary gland. Prior to these contributions virtually nothing was known about that remarkable structure, except the fact of its existence. Clinically, it was soon recognized that dwarfism was not an essential component of the adiposogenital syndrome, since cases unassociated with it were not lacking. As more and more examples came to be recognized and studied at autopsy, the finding of a neoplasm destroying the hypophysis, or its vicinity, became an almost constant feature.

Adiposogenital dystrophy is so well recognized clinically that it calls for but the briefest description. The outstanding sign is an obesity which is especially accentuated over the girdle region, hips, thighs and breasts. The distal extremities are often spared. In the male, it is accompanied by hypoplasia or aplasia of the external and internal genital apparatus. The penis is small, usually embedded in a mound of pubic fat. The testes are likewise diminutive. At autopsy, a small prostate has been described frequently. Microscopically, the testes show an absence of, or diminution in, the activity of spermatogenesis, as well as a reduction in the number of interstitial cells. In the female the obesity is of similar distribution. The uterus is infantile. Ovarian changes are rather inconstant. Amenorrhea or oligomenorrhea is a striking clinical symptom. In both sexes, the symptom complex is often completed by somnolence, mental apathy, subnormal temperature, pallor, headache, and anaphrodisia or sterility. Polyuria or diabetes insipidus is often present.

As so-called typical cases are analyzed, it becomes apparent that no case is truly typical because the syndrome is never uniform. This lack of uniformity is dependent on a variety of factors: (1) The pituitary lesion is never uniform in size or extent and, one might add, in nature; (2) the symptoms vary, depending on the time of onset of the disorder with respect to puberty; (3) secondary alterations in other endocrine glands are likewise variable and influence the clinical picture.

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Dr. Henry J. Spencer, Director of the Second Medical Division, Bellevue Hospital, gave the author permission to report this case.

1. Marie, P.: Sur deux cas d'acromégale hypertrophie singulière non-congénitale des extrémités, Rev. de méd., Paris **6**:297, 1886.

2. Fröhlich, A.: Ein Fall von Tumor der Hypophysis Cerebri ohne Akromegalie, Wien. klin. Rundschau **15**:883, 1901.

At present it has become the fashion to classify pituitary disorders into disturbances of the anterior, posterior and intermediary lobe which are hyperfunctional or hypofunctional, preadolescent or postadolescent, and as occurring in the male or in the female.

Before the era of experimental hypophysectomy the functions of the various lobes of the pituitary body and its intimately adjacent structures were largely interpreted on the basis of destructive anatomic lesions, but these were so variable in extent that it was often impossible to ascribe any supposed function to a particular lobe. Thus a variety of views was held to explain the pathogenesis of the symptoms: 1. The various symptoms of pituitary disturbances were the result of excessive secretion. Adenomas of the pituitary were frequent findings. 2. The condition was the result of diminished secretion associated with a destructive lesion of the pituitary body and its environs. 3. The symptoms were caused by pressure on adjacent areas of the brain, notably on the infundibulum and hypothalamus. Such effects might be paralytic, stimulatory or both. 4. The symptoms, especially the obesity, were the result of secondary changes in other organs of internal secretion, notably the thyroid and the genitalia. Thus, adiposogenital dystrophy was a kind of second-hand hypothyroidism or hypogenitalism.

The third view was espoused in general by Erdheim,[3] Aschner[4] and others, who may perhaps be regarded as pioneers in attributing to the hypothalamus the master rôle in the symptomatology of these apparently hypophyseal disorders. Cushing[5] pointed out that recognition is due to Bramwell[6] for the priority of this view: as early as 1888, he suggested that the obesity and polyuria accompanying tumors of the pituitary body were probably the result of pressure on the surrounding cerebral tissue.

The era of experimental hypophysectomy followed, inaugurated, I believe, by Paulesco[7] and later carried on largely in this country by Cushing and his associates.[8] At this time, it seemed to be the unanimous opinion that total extirpation of the gland was promptly fatal, death occurring in a few days with a characteristic train of symptoms called cachexia hypophyseopriva. Life was believed to be sustained by leaving intact a small residuum of the anterior lobe. In animals the hypopituitary state which resulted from subtotal extirpation of the gland was much like that of adiposogenital dystrophy; that is, adiposity, sexual hypoplasia and functional inactivity, somnolence, subnormal temperature and polyuria, all of varying degree, developed. Cushing[8a] originally believed that the adiposity was an effect of deficiency of the anterior lobe. When, however, in later experiments[8b] the animals showed a high tolerance for carbohydrate, which was rather strikingly lowered by treatment with extracts of the posterior lobe,

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3. Erdheim, J.: Ueber Hypophysengangesgeschwülste und Hirncholesteotome, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **113**:537, 1904.

4. Aschner, B.: Demonstration von Hunden nach Exstirpation der Hypophyse, Wien. klin. Wchnschr. **32**:572, 1910.

5. Cushing, H.: Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 18.

6. Bramwell, Byrom, quoted by Cushing,[5] p. 18.

7. Paulesco, N. C.: L'hypophyse du cerveau, Paris, Vigot Frères, 1908.

8. (*a*) Crowe, S. J.; Cushing, H., and Homans, J.: Experimental Hypophysectomy, Bull. Johns Hopkins Hosp. **21**:127, 1911. (*b*) Goetsch, E.; Cushing, H., and Jacobson, C.: Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, ibid. **22**:165, 1911.

the adiposity was classified as a deficiency of the posterior lobe, and the posterior lobe was credited with a rôle in the regulation of carbohydrate metabolism.

The fatal results of total extirpation were always doubted, however, and it was suggested that death was due to injury of the overlying brain stem. Indeed, the pathologists who had attributed the effects of destructive lesions of the pituitary body to pressure on the adjacent hypothalamus must always have doubted the interpretations of Cushing's experiments and must have thought that this so-called hypopituitary state was really a hypothalamic state. Still it is safe to say that Cushing's conclusions in allocating to the anterior lobe the regulation of growth and of sex activity, and to the posterior lobe an influence on carbohydate metabolism, water metabolism and, perhaps, sleep, dominated all others, although it must be admitted that the vital importance of the pituitary body in maintaining life in dogs was readily disproved by Sweet,[9] Dandy [10] and others.

Later, Camus and Roussy [11] presented conclusions drawn from researches in which they performed a long series of experimental hypophysectomies on dogs; in other instances they produced destructive lesions in the tuber cinereum and in the hypothalamus. Their work was presented in great detail, but for the purpose of the present discussion it may be summarized, as follows: 1. Complete removal of the hypophysis is not fatal, unless the region of the infundibulum and the tuber cinereum is accidentally injured. Many animals survived total extirpation of the gland, whereas apparently superficial injury to the region of the tuber cinereum proved fatal. 2. Experimental lesions at the base of the brain produce polyuria, arrest of sexual development, genital atrophy, adiposity and an increased tolerance for carbohydrates.

Virtually every supposed function of the hypophysis, with the possible exception of regulation of skeletal development, was thus attributed to the hypothalamus.

The independent conclusions of Bailey and Bremer [12] differed in no great wise from those of Camus and Roussy, adiposogenital syndromes being produced in dogs by hypothalamic punctures without damage to the pituitary body. The pituitary body, and more especially the posterior lobe, seemed to have been well shorn of its functions.

Still more recently, Smith [13] performed hypophysectomies on rats, employing this animal because its hypophysis is separated from the base of the brain by a prolongation of the dura. Transphenoidal hypophysectomies in rats did not pro-

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9. Sweet, J. E., and Allen, A. R.: The Effect of the Removal of the Hypophysis in the Dog, Ann. Surg. **58**:485, 1913.

10. Dandy, W. E., and Reicher, F. L.: Studies on Experimental Hypophysectomy: I. Effect on the Maintenance of Life, Bull. Johns Hopkins Hosp. **37**: 1, 1925.

11. Camus, J., and Roussy, G.: Diabetes Insipidus, Glycosuria and Those Dystrophies Considered as Hypophyseal in Origin, Endocrinology **4**:507 (Oct.) 1920. Syndrome adiposogénitale et diabète insipide expérimentale, Compt. rend. Soc. de biol. **85**:296, 1921. Polyurie expérimentale par lésions de la base du cerveau; la polyurie hypophysaire, ibid. **75**:628, 1913; Localisation anatomique à la base du cerveau des lésions qui provoquent la polyurie chez le chien, ibid. **76**: 877, 1914.

12. Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus and Genital Atrophy, Endocrinology **5**:761, 1921.

13. Smith, P. E.: Hypophysectomy and a Replacement Therapy in the Rat, Am. J. Anat. **65**:205, 1930.

duce sudden death. However, in immature rats, dwarfism, genital atrophy and slight obesity did develop. When the hypophysis was destroyed by injections of chromic acid, a marked degree of adiposity developed, the other results remaining the same. Smith attributed the marked adiposity in the latter set of experiments to diffusion of the chemical along the pituitary stalk to the diencephalon, where it presumably destroyed some centers.

The immediate effect of these briefly quoted experiments was to divest the hypophysis of nearly every one of its supposed functions, a rather shocking disturbance to those who had been brought to recognize in that gland a structure of vital importance. How to reconcile these apparently inharmonious conclusions has taxed the meditative and investigative faculties of many a thinker. However, the combined resources of anatomy, physiology and pathology have already shed sufficient light on the problem so that it may be regarded as, at least, partially solved.

1. Pathology: Notwithstanding the opinion of Erdheim,[3] who maintained that the majority of symptoms of hypopituitarism were the result of hypothalamic pressure, it must be admitted that many times an adiposogenital syndrome, with or without polyuria, resulted from strictly intrasellar tumors. At least, a few examples are on record in which the tuberal region was subjected to serial sectioning without evidence of nuclear degeneration.

2. Anatomy: The pituitary body is related to the hypothalamus by way of a blood supply and a nerve supply. The arterial blood supply of the pituitary body is derived both from the internal carotid and from a small vessel which enters the stalk near the tuber cinereum. The venous drainage consists of, among other structures, a system of portal veins discovered by Popa and Fielding,[14] which drains the sinusoids of the anterior lobe and the pars intermedia.

Herring[15] originated the hypothesis that the secretions from the posterior lobe found their way to the infundibulum, whence they were discharged into the third ventricle to exert their activity on nuclei in the floor of that structure. The intermediary pathway down the stalk has been a subject of some speculation, but it is not unlikely that the hypophyseoportal veins referred to by Popa and Fielding partially provide the solution.

3. Physiology: The researches of Karplus and Peczenik[16] have taught that the hypothalamic centers probably regulate the activity of posterior pituitary secretion. Stimulation of certain nuclei in the floor of the third ventricle increased the concentration of a substance resembling the hormone from the posterior lobe in the fluid of the ventricles.

Moreover, Cushing[5] has, in a sense, substantiated Herring's hypothesis by showing that the characteristic pharmacologic effects of the hormone from the posterior lobe are exerted after intraventricular rather than after subcutaneous administration. Hence, the failure to obtain satisfactory therapeutic effects from pituitary therapy is probably due, in part, to the route of administration.

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14. Popa, G., and Fielding, U.: The Vascular Link Between the Pituitary and the Hypothalamus, Lancet **2**:238, 1930.

15. Herring, P. T.: The Histological Appearances of the Mammalian Pituitary Body, Quart. J. Exper. Physiol. **1**:121, 159, 1908.

16. Karplus, I. P., and Peczenik, O.: Uber die Berinflussung der Hypophysentätigkeit durch die Erregung des Hypothalamus, Arch. f. d. ges. Physiol. **225**: 654, 1930, cited by Cushing,[5] p. 61.

The experiments of Raab[17] have largely elucidated the rôle of the hormone from the posterior pituitary lobe in the regulation of fat metabolism, for they indicate that treatment with pituitary preparations regularly causes a disappearance of fat from the circulating blood. Large subcutaneous doses of several cubic centimeters are required to produce these effects, whereas small intraventricular doses produce more striking and more lasting effects. Raab showed further that this effect of pituitary preparations could be abolished by mechanical destruction of the midbrain or by the previous administration of certain antipyretic coal tar products, which probably paralyze the mesencephalic centers. To quote Raab freely: Pituitrin promotes the absorption and destruction of circulating fat by a nervous path starting in the tuber and ending in the liver. Any disturbance in the operative activity of the pituitary mesencephalic system will leave these amounts of fat undestroyed. They will be stored in the tissues and consequently lead to obesity.

According to Raab, obesity may be hypopituitary or mesencephalic in origin, and the concept might be enlarged on; it is likely that all the symptoms which characterize the hypopituitary state may have their origin in diencephalic or in pituitary destructive lesions. Such a point of view, which I believe is that of Cushing, Raab and others, would really link the pituitary body and the hypothalamus into a virtually interdependent neuro-endocrine system, disturbance within which at various places in the chain would result in modified hypopituitary symptoms. Thus, too, would be explained typical cases of adiposogenital dystrophy occurring as a sequel of epidemic encephalitis, in which, at autopsy, inflammatory lesions of the midbrain and brain stem without pituitary lesions are found.

Many gaps remain to be filled in the intricate relationship between the component parts of this neuro-endocrine system, but the theory possesses so much experimental and pathologic support that it cannot fail to be preferred to the disquieting views of the hypothalamists who would, perhaps a bit ruthlessly, deny even the semblance of importance to that most ancient of the endocrine glands, the pituitary body.

REPORT OF A CASE

This case is reported because in it there occurred a selective destruction of the posterior lobe of the pituitary body with minimal involvement of the anterior lobe. Nature, it was thought, had accomplished what the physiologist had long hoped to accomplish.

History.—A. K., aged 32, a Russian Jew, was admitted to the Metropolitan Hospital on June 5, 1929, complaining of gradually increasing obesity, headache, polyuria, dyspnea, somnolence and bleeding varicose veins. The patient had arrived in this country from Russia at the age of 15. At that time he appeared normal in size and development, and weighed 160 pounds (72.57 Kg.). During the subsequent eleven years he gained weight slightly, reaching 200 pounds (90.72 Kg.) at the age of 26. During this time he was disinclined to work and lazy, and he possessed an enormous appetite for rich and heavy food. From the age of 26 to 32 he gained weight rapidly and came under observation at various hospitals to which he was admitted, until the time of his death, seven years later. At the time of his first admission in June, 1929, he weighed 304 pounds (137.89 Kg.).

17. (*a*) Raab, W.: Pituitrin: Fettstoffwechselwirkung und vegetatives Nervensystem, Ztschr. f. d. ges. exper. Med. **62**:366, 1928. (*b*) Raab, W.: The Rôle of the Posterior Pituitary Hormone in Fat Metabolism, Endocrinology **14**: 385 (Nov.) 1930.

He then complained of obesity, polyuria and somnolence. The last symptom was so evident that the patient feared to sit down, knowing his tendency to lapse into a sound sleep. Headache localized above the glabella and in the temporal fossa was also a prominent symptom. The immediate cause for admission was bleeding from ruptured varicose veins of the left leg.

He was readmitted on Nov. 10, 1929, and discharged on Sept. 28, 1930, complaining of dyspnea and obesity. The other symptoms were practically unchanged, but the dyspnea was more pronounced. At this time he weighed 340 pounds (154.12 Kg.), but he lost 32 pounds (14.51 Kg.) under treatment. During this time he had several attacks of grip and pharyngitis.

The third admission was on Oct. 21, 1930. He was discharged on Nov. 6, 1931. At this time he again suffered from an acute pharyngitis and from an infectious arthritis involving the knees and elbows, as well as from the other symptoms. The weight was recorded as "very fat."

On a subsequent admission the patient complained more and more of cardiac symptoms, namely dyspnea and cyanosis. Severe frontal headaches developed. There eventually appeared a slight degree of exophthalmos, which at the time of death, on Feb. 25, 1932, had become more pronounced. The weight meanwhile had reached 450 pounds (204.12 Kg.). The immediate cause of death was congestive heart failure.

The patient had scarlet fever in childhood; otherwise, the previous history was without significance. A sister was also obese, as was the patient's father. No other details of the family history were recorded.

Physical Examination.—The outstanding feature was the excessive obesity. Fat was present externally all over the body, involving the head, neck, girdle area, breasts, thighs and lower extremities, which were rather short. Varicose veins were present on both legs. The abdomen was pendulous, the skin being folded several times and the contact surfaces being excoriated. The height was 5 feet and 4 inches. Slight exophthalmos was present at the later admissions. The turbinates were congested, and there was a slight nasal discharge. The retinal vessels were slightly tortuous and engorged. The tonsils were enlarged; the pillars and uvula were congested and edematous. Many teeth were missing, the remaining ones being carious. The penis and scrotum were described as "small."

Laboratory Findings.—The urine was concentrated and generally normal. Glycosuria was never found. The blood pressure was always elevated, but showed considerable fluctuations. On admission it was 138 systolic and 105 diastolic, but reached heights of 210 systolic and 140 diastolic. At the time of death it fell to 110 systolic and 80 diastolic. The temperature was generally normal, except for febrile periods associated with infections. Terminally, it was 98 F. by rectum. A Wassermann test gave negative results. Roentgen examination of the chest, sinuses and skull was unsatisfactory because of the extreme girth of the chest and head. Estimations of the sugar, total nitrogen and creatinine of the blood gave normal readings. Two studies of the basal metabolism in 1931 showed readings of plus 12 and plus 13. The results of the dextrose tolerance test were: fasting, 100 mg.; one hour, 202 mg.; two hours, 240 mg.; four hours, 780 mg.

Autopsy.—Necropsy was performed within twelve hours after death. The anatomic diagnoses were: hypopituitary adiposity; cyst of the posterior lobe of the pituitary body; hypertrophy and dilatation of the heart; thrombosis of the right auricular appendage; fatty invasion of the myocardium; coronary arteriosclerosis; atherosclerosis of the aorta; chronic passive congestion of the lungs, liver, spleen, kidneys and gastro-intestinal tract; fat invasion of the pancreas; hydrocele of the right tunica vaginalis.

There was marked adiposity, as described in the physical examination. The panniculus adiposus measured 8 cm. in thickness. The omentum, mesentery and appendices epiploicae were greatly laden with fat. There was also a marked amount of mediastinal fat covering the pericardium and epicardium. No thymic remains were seen. No fluid was present in either pleural cavity.

The pericardial cavity contained 30 cc. of straw-colored fluid. The heart was enormously enlarged and dilated, and weighed 695 Gm. The right auricular appendage contained several firm adherent antemortem thrombi. The tricuspid ring admitted four fingers. The right ventricle was dilated and hypertrophied. The left auricle was also dilated. The mitral valve contained several atheromatous patches. The left ventricle was markedly hypertrophied and infiltrated by strands

Fig. 1.—Photomicrograph of the pituitary gland, sagittal view, showing the irregular, ragged destruction of most of the posterior lobe. Hematoxylin-eosin stain; reduced from × 10.

of invading epicardial fat. The coronary vessels showed numerous eccentric atheromas.

Both lungs were congested and firm. The pulmonary arterioles were occluded by small gray thrombi. Infarcts were present in both lower lobes.

The liver was moderately enlarged and extended 3 inches below the costal margin. It possessed a modified nutmeg appearance, but was not particularly fatty in appearance.

The spleen weighed 610 Gm. and was greatly enlarged. The pulp was congested, but soft.

The kidneys were enlarged and weighed 540 Gm. They were markedly congested, but otherwise normal.

The suprarenal glands were of natural size. The cortex measured 2 mm.; the medulla was brown and semisolid.

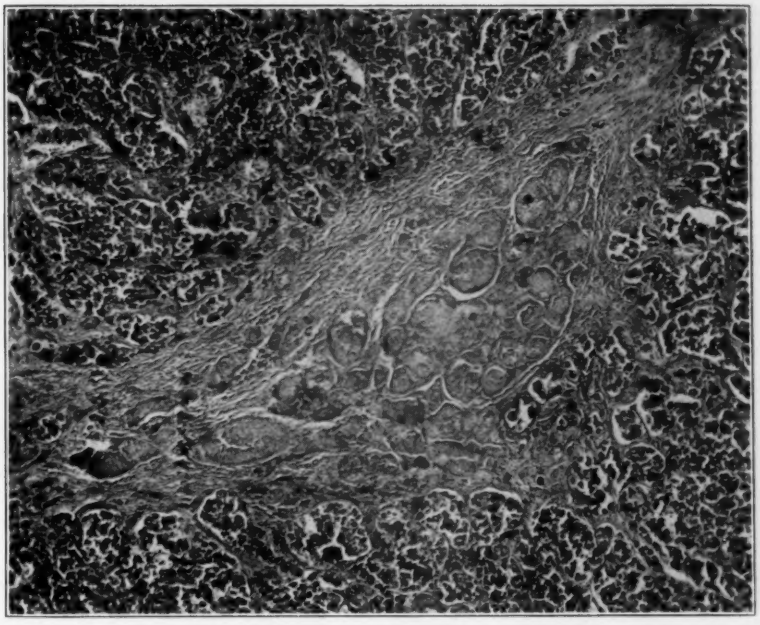

Fig. 2.—Photomicrograph of the anterior pituitary lobe, showing an area of hyalinization of the acini and surrounding sclerosis. Remnants of degenerating acini may be seen in the periphery of the sclerotic area. Hematoxylin-eosin stain; approximately × 100.

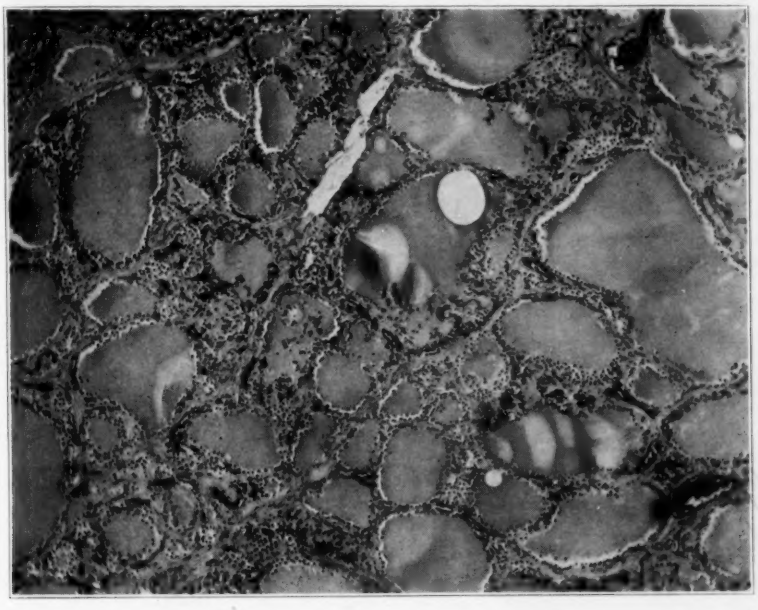

Fig. 3.—Photomicrograph of a section of the thyroid gland. There is slight colloid transformation. Hematoxylin-eosin stain; approximately × 100.

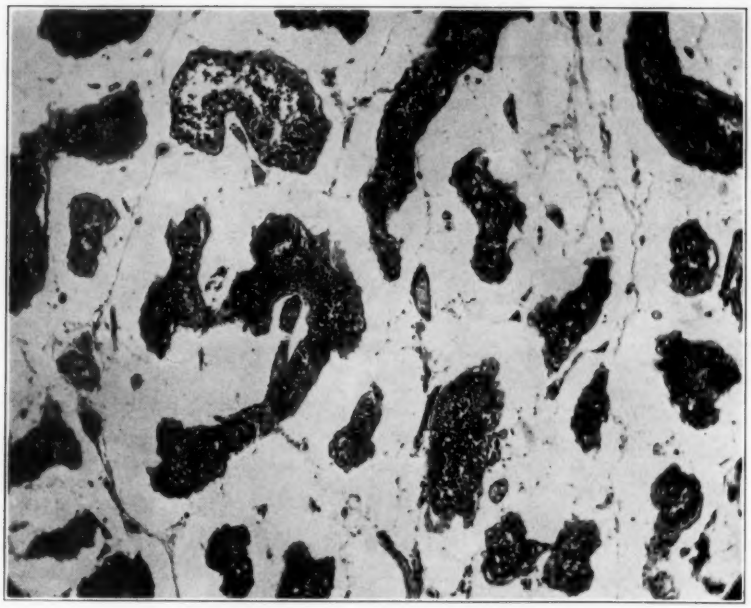

Fig. 4.—Photomicrograph of testes. Note the irregular appearance of the tubules and the wide separation from one another. Note also the virtual absence of interstitial cells. Hematoxylin-eosin stain; × 100.

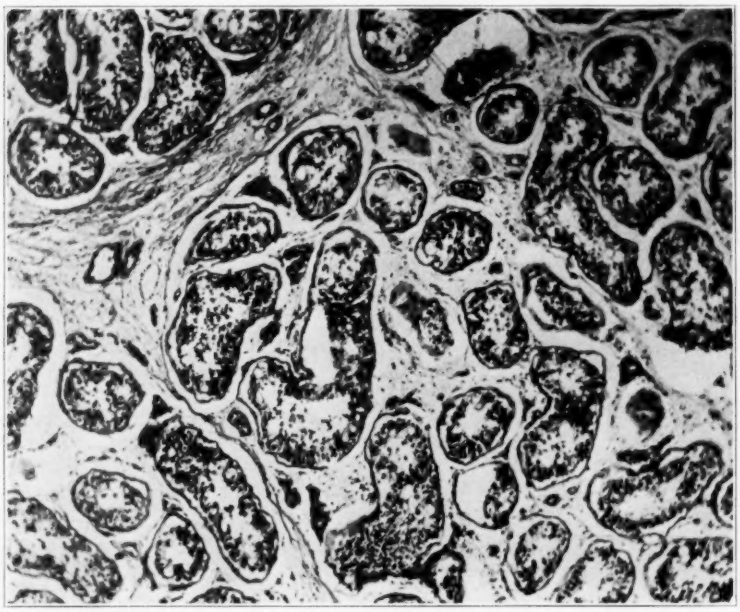

Fig. 5.—Photomicrograph of testes of a man, aged 37, showing for comparison a relatively normal structure. Note the increased size and numbers of tubules and the great number of interstitial cells. Hematoxylin-eosin stain; × 100.

In the gastro-intestinal tract there was marked congestion of the mesenteric veins. The gastric mucosa was hypertrophic and covered with mucus.

The pancreas was largely replaced by fat.

The bladder, prostate, seminal vesicles, testes and thyroid appeared natural on gross examination.

The skull appeared normal. The brain was sectioned in the routine manner and appeared entirely normal. The pituitary gland was about 1 cm. in diameter; it appeared normal until it was sectioned, when a cyst, about 0.7 mm. in diameter, was found occupying the posterior lobe; the cyst contained whitish-gray granular material.

Microscopic Examination.—Heart: Sections showed an increase of fat in the subepicardial and perivascular fascial spaces. The muscles were hypertrophied and throughout appeared fragmented; they had lost their striations. Fat stains of frozen sections failed to show any fatty degeneration of myofibrils. The diagnosis was hypertrophy; fatty invasion; myocardial degeneration.

Lungs: There was characteristic chronic passive congestion with "heart failure cells." Numerous sections showed infarcts. The diagnosis was: chronic passive congestion; infarcts.

Liver: There was typical central congestion and atrophy. No fatty degeneration was present. The diagnosis was that of chronic passive congestion.

Spleen: The capsule appeared thickened; the endothelial sinuses were congested. The arterioles were thickened and hyalinized. The diagnosis was chronic passive congestion; arteriosclerosis.

Kidneys: There was intense congestion of the arterioles and the capillaries of the glomerular tufts. There was a marked amount of tubular degeneration. Frozen sections and fat stains gave negative results for lipoid material. The diagnosis was congestion; tubular degeneration.

Testes: The arterioles were congested. The tubules were reduced in size and number. They were widely separated and occurred less frequently in a low power field than did those of a control subject of approximately the same age. The interstitial cells were likewise fewer than those of a control subject. Active spermatogenesis was present, however, and mature spermatozoa were present in the tubules.

Thyroid: Many sections from several areas revealed a fairly uniform colloid transformation. The acini were dilated and the epithelium was flattened. Occasionally a small papillary projection into an acinus was visible. The interstitial tissue was increased, but no lymphocytes were present. The colloid was dense and highly refractile in appearance. The diagnosis was colloid goiter.

Pancreas: Marked postmortem autolysis was present.

Suprarenal Gland: This was, unfortunately, lost.

Pituitary Gland: This was cut sagittally to show the anterior lobe, the posterior lobe and the stalk. After several routine sections had been cut, the remainder of the gland was subjected to serial sectioning. A few sections were lost. The anterior lobe showed the usual admixture of chromophobe and chromophile cells. The colloid content appeared increased both in the sinusoids and in the alveolar lumen. A small island of connective tissue in which some of the acini appeared to be undergoing hyaline transformation occurred throughout many sections. The process resembled an area of replacement fibrosis. The pars intermedia and pars tuberosa appeared natural. There was an irregular ragged-edged destruction of

approximately three quarters of the posterior lobe. A small rim of remaining tissue appeared entirely natural. The stalk contained numerous colloid masses, as well as columns of cells resembling those present in the pars intermedia. The vessels showed no thrombotic changes; the media in places appeared slightly thickened and the elastica was occasionally reduplicated.

COMMENT

At present, many gaps exist in the knowledge of the pathologic histology of the pituitary gland and of the diseases to which this important organ is heir. Following Fröhlich and Marie, many adenomatous tumors came to be recognized clinically and pathologically. Histologically, it has been possible to separate these into at least three types, each of which is derived from progenitor cells in the anterior lobe. Acromegaly is thus known to be synonymous with postadolescent pituitary acidophilism, and the underlying condition may be an adenoma, adenocarcinoma or benign hyperplasia of the acidophilic cells. The more frequent chromophobe adenomas are now known to produce most, if not all, of their effects by destroying the normal elements of the anterior and posterior lobe, as well as "neighborhood" effects due to pressure on surrounding structures, principally the optic nerves and the diencephalon. Recently,[5] a new and variable syndrome, which is believed to be dependent on pituitary basophilism, has come to be recoginzed and represents a new form of hyperpituitarism.

Various other tumors are now known to destroy, partially or totally, the pituitary body and its environs, notably the cystic and solid tumors arising from the remnants of the craniopharyngeal duct, first identified by Erdheim.[3] These cysts and tumors, like the chromophobe adenoma, produce symptoms because of their destructive pressure effects. Naturally, the symptoms of these extensive destructive tumors are variable.

In several instances, acute infection has been shown to destroy the pituitary body. Such infections are usually gross or microscopic abscesses; to date not a few have been reported by Plaut,[18] Simonds [19] and others.[20] Plaut studied the hypophysis in thirty-five cases of pyemia and found it altered seventeen times. Changes in the posterior lobe were generally inflammations, with necroses in the anterior lobe. Simonds [19b] reviewed the literature on the subject and showed that before him Heslop,[21] Glinski [22] and others had described abscesses of the pituitary body. Simonds [19b] found seven abscesses of the pituitary gland in routine studies

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18. Plaut, A.: Hypophysisbefunde bei akuten Infektionskrankheiten, Klin. Wchnschr. **1**:552, 1922.

19. (*a*) Simonds, J. P.: Some Lesions of the Hypophysis, Tr. Chicago Path. Soc. **11**:183, 1921; (*b*) Studies on the Pathology of the Hypophysis: Abscess of the Hypophysis, Endocrinology **9**:117, 1925. (*c*) Simonds, J. P., and Brandes, W. C.: The presence of Abnormal Cells in the Posterior Lobe, Am. J. Path. **1**: 209, 1925.

20. Fahr, T.: Ein Fall von akuter diffuser Hypophysites, Deutsche med. Wchnschr. **49**:497, 1923.

21. Heslop, T. P.: A Case of Hypertrophy with Abscess of the Pituitary Body, Dublin Quart. J. Med. **6**:466, 1848.

22. Glinski, L. K.: Anatomische Veränderungen der Hypophyse, Przegl. lek., (Krakow) 1913; abstr., Deutsche med. Wchnschr. **39**:473, 1913.

of two hundred serially sectioned pituitary glands. Experimentally, Adachi and Tanaka [23] infected guinea-pigs with Bacillus diphtheriae and discovered various necrotizing alterations in the pitutitary gland. Simonds and Brandes [19c] have also found histologic round cell infiltration in the posterior lobe in a high percentage of instances, which would certainly suggest that this lobe is not infrequently the site of chronic inflammations.

Now in large clinics for the diagnosis of endocrine disturbances, such as those of Rowe and Lawrence [24] and of Engelbach [25] and Tierney,[26] the nonneoplastic types of pitutitary disorders are at the head of the list in point of percentage and frequency. Such nonneoplastic dyspituitary states are called functional because of the present state of ignorance which exists regarding alterations of the pituitary body or brain stem which give rise to them. This ignorance is due to the paucity of postmortem information. Engelbach estimated that 95 per cent of pituitary disturbances are functional and only 5 per cent neoplastic, but it is safe to say that until recently most attention was riveted on the neoplastic types of pituitary disorder whose causes have already been briefly mentioned.

These hypopituitary dysfunctions give a variety of symptoms, among which obesity, menstrual disturbance, headache and somnolence are probably the most frequent, but it may safely be said that they imitate every variety of neoplastic disorder. In the anamnesis of these subjects a history of recurrent infections is so frequent that it undoubtedly indicates either: (1) that acute infections frequently give rise to hypopituitary and dyspituitary states, or (2) that persons with these disorders are highly susceptible to recurrent acute infections. The probability is that both relationships maintain, but I believe that the former represents the more important relationship.

Thus, 50 per cent of Rowe and Lawrence's patients stated that they had acute tonsillitis, 37 per cent mumps, 19 per cent scarlet fever and 17 per cent influenza.

These figures, except those for tonsillitis might well be casually dismissed by a critical commentator as differing but slightly from the normal incidence of these diseases, but it is highly significant that in many protocols the onset of symptoms coincides with convalescence from an acute infection and that such a history recurs so frequently that it cannot be lightly disregarded. Indeed, infection must be seriously accepted as a probable cause of abnormal pituitary states.

Unfortunately, clinicopathologic correlations of these disorders are entirely lacking because the diseases are not in themselves fatal. None the less, when coupled with the knowledge of frequent acute and chronic inflammatory changes in the hypophysis and rather few carefully studied cases, it admits of but one conclusion, namely, that more frequently than is supposed the pituitary gland is modified by acute or chronic infections and that these modifications play an important rôle in the causation of pituitary disorders—far more important, no doubt, than heredity.

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23. Adachi, O., and Tanaka, K.: Verhandl. d. jap. path. Gesellsch. **6**:23, 1916.

24. Rowe, A. W., and Lawrence, C. H.: II. The Pituitary, in Collected Publications from the Robert Dawson Evans Memorial for Clinical Research and Preventive Medicine; No. 1, Endocrine Studies, Boston, F. J. Barnard & Company, Inc., 1929.

25. Engelbach, W. W.: Diseases of the Pituitary Body, in Cecil, R. L.: Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1930, p. 1168.

26. Tierney, J. L.: Classification and Treatment of Hypophyseal Disorders, Endocrinology **7**:536, 1923.

Falta [27] reported an example of a hazelnut cyst of the pituitary gland occupying the central portion of the gland and compressing both lobes. It occurred in a tailor, aged 55. The onset of symptoms of pituitary disturbance had taken place ten years before admission and was accompanied by a continued high fever. The cyst was lined by endothelium and full of shreds. The symptoms were progressive cachexia and diminution of sexual function. Falta stated: "The disease was ushered in with an unknown infectious process. Perhaps this also affected the hypophysis and gave occasion for the cyst formation."

Embolic infarctions of the pituitary have been described in connection with hypophyseal cachexia or Simmonds' disease in the course of tuberculous, syphilitic and septic infections.[28] It is not unlikely that the necrotic cavity described in this case represents some variety of old embolic destructive process, although I am unable to prove this from the serial sections.

Correlation of the Symptoms with the Lesion.—The symptoms which the patient exhibited correspond in a general way with symptoms of deficiency of the posterior lobe. The relationship of adiposity to deficiency of the posterior lobe has already been discussed.

Polyuria: The antidiuretic effects of extracts of the posterior lobe are well known, although in earlier days some ascribed to these extracts an opposite diuretic effect. True diabetes insipidus has been produced experimentally by lesions of the stalk in which the tuberal region was not injured and by superficial injuries in the infundibulotuberal region (Camus and Roussy). On the other hand, Marañon [29] reviewed the reports of autopsy in thirty-two cases of true diabetes inspidus, and in every case he found a lesion of the posterior lobe.

In Cushing's subtotal hypophyseal extirpations in the dog, diuretic responses were usually obtained, although these were less striking than those of true diabetes insipidus. The long history of polyuria in my patient would seem to be explained by a defect of the posterior lobe, and the nature of this polyuria, which was probably neither as excessive in amount nor associated with as low a specific gravity, would correspond closely to that obtained by experimental injury of the posterior lobe.

In the absence of careful studies of intake and output one might also ascribe the polyuria to an underlying diabetes mellitus. The polyuria of diabetes mellitus is, however, associated with hyperglycemia and glycosuria and is probably an expression of the diuretic effect of sugar. In attributing the polyuria to deficiency of the posterior lobe I am urged by the fact that during the early years of illness polyuria was present, although unaccompanied by either glycosuria or hyperglycemia.

Somnolence: Pathologic somnolence amounting, as in this case, to a true narcolepsy is a not infrequent symptom of pituitary disorder, although many would attribute its occurrence exclusively to lesions in the brain stem. Somnolence has been described in association with strictly intrasellar destructive processes. It was a notable symptom in Cushing's subtotal extripations, although, strangely, it

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27. Falta, W.: The Ductless Glandular Diseases, Philadelphia, P. Blakiston's Son & Company, 1915, p. 312.

28. Simmonds, M.: Ueber embolische Prozesse in der Hypophysis, Virchows Arch. f. path. Anat. **217**:226, 1914.

29. Marañon, G.: Diabetes Insipidus as a Hypopituitary Syndrome, Endocrinology **5**: 159, 1921.

was absent in the one instance in which a strict removal of the posterior lobe was attempted. This case would appear to confirm the fact that pathologic somnolence may occur as a symptom of deficiency of the posterior lobe in the absence of a tuberal destructive lesion.

Headache: In recent years much has been written about pituitary types of headache. Originally attributed to pituitary tumors, their occurrence in the absence of tumors is now well known. Indeed, these types of headache occurred in the histories of 34 per cent of Rowe and Lawrence's cases, most of which were examples of functional pituitary disturbance. The characteristic location "deep in the head between the eyes," or localized over the occiput, is well known. In women, menstrual headaches are now regarded as pituitary in origin, and even migraine has been regarded as a pituitary dysfunction.

Headache caused by pituitary disturbance is said to be aggravated by the ingestion of carbohydrates and relieved by the administration of preparations of whole gland. It also responds to hypodermic injections of extracts of the anterior lobe, so that the participation of the posterior lobe has been ignored.

Pardee [30] attributed the headache to slight functional swelling of the gland with resultant stretching of the capsule. It certainly occurs without general increase in intracranial pressure.

In my patient, the headache could perhaps with equal validity be attributed to hypertension, although its persistent nature before hypertension was well developed would seem to argue for a pituitary basis. Headaches due to hypertension are notably associated with the more elevated grades of blood pressure.

Hypertension and Exophthalmos: These cannot be explained by a lesion of the posterior lobe, nor can they be explained by secondary thyroid changes. As to secondary suprarenal changes, I am in no position to state. Hypertension and exophthalmos are notable symptoms in the newly recognized syndrome of pituitary basophilism.

Exophthalmos finds a plausible explanation on mechanical grounds as due to excessive accumulations of retro-orbital fat. On the other hand, it is not inconceivable that both exophthalmos and hypertension represent an overstimulation of the sympathetic nervous system. If, as Cushing [5] suggested, the hormone from the posterior lobe acts on a hypothetic parasympathetic center in the base of the brain, a destructive lesion might well upset the balanced antagonism between these two components of the autonomic nervous system, with an overemphasis of the sympathetic. This is admittedly an imaginative concept, yet it is not without its temptations.

Tolerance for Carbohydrate: An abnormal elevation of tolerance for carbohydrate has long been recognized as a symptom of diminished function of the posterior lobe. That this tolerance can be diminished by administration of extracts of the posterior lobe was shown by Cushing and his co-workers. As mentioned, the obesity of pituitary disorder has been explained on the basis of abnormal carbohydrate metabolism, the carbohydrate being converted into fat. Hence, in treatment for hypopituitary obesity many clinicians are concerned with limiting the carbohydrate rather than the total caloric intake.

A test for carbohydrate tolerance performed about a year before the patient's death showed a marked reduction, the blood sugar reaching a height of 7.8 per cent without the appearance of glycosuria. This is contrary to what would have been expected. Experimentally, a similar behavior of the blood sugar is obtained

30. Pardee, I. H.: Pituitary Headaches and Their Cure, Arch. Int. Med. **23**: 174 (Feb.) 1919.

in pancreatectomized dogs, and clinically it is sometimes observed in advanced diabetes mellitus. Some degree of diabetes mellitus must undoubtedly have been present although the persistent normal values for blood sugar are difficult to explain. Lessened permeability of the kidneys to excretion of sugar must undoubtedly have been present as an added factor. This diabetes mellitus may represent a terminal exhaustion of an overworked pancreas and is occasionally reported in hypopituitary syndromes.

Genital Atrophy: There has been ample experimental proof since the experiments of Cushing [8] on the dog and the more recent, and perhaps better controlled, experiments of Smith [13] on the rat that the genital atrophy observed in hypopituitary states represents an effect of deprivation of the anterior lobe. The degree of genital atrophy varies according to whether the animal or human being is preadolescent or postadolescent.

When, therefore, Camus and Roussy [11] and Bailey and Bremer [12] showed that atrophic genital effects were reproduced in dogs which had sustained superficial injuries to the hypothalamic regions without pituitary destruction, it seemed as though the anterior, as well as the posterior lobe, was deprived of an important function. Without entering into a discussion which would go too far afield, it may be stated that the anterior pituitary lobe probably shares with the posterior lobe a participation in a pituitary-mesencephalic system, and it is highly probable that the hormones of the anterior lobe influence one or more sex centers located somewhere in the interbrain.

I should therefore correlate the genital atrophy with the degenerative and sclerotic changes in the anterior lobe of the pituitary body. It might well be argued, however, that a single lesion in the brain stem would explain both the genital atrophy and the symptoms attributed to defect of the posterior lobe.

SUMMARY AND CONCLUSIONS

1. In a man with a ten year history of progressive adiposity, with later development of headache, polyuria, somnolence, hypertension, exophthalmos and genital atrophy, a cystlike destruction of the posterior lobe of the pituitary gland was found at autopsy. The region of the third ventricle showed no gross deformity or destructive lesions, although microscopic examination of the region was not performed.

2. No explanation for this peculiar destructive lesion was found. The probability of some earlier postinfectious embolic process was considered most likely.

3. An area of sclerosis was found in the anterior pituitary lobe. Its significance, too, is unknown.

4. A hypothetic attempt has been made to correlate the lesions with postinfectious functional hypopituitary states whose pathology is at present largely unknown.

5. Following the views of Cushing, an attempt has been made to explain the predominant symptoms on the basis of deficiency of the posterior lobe—including a symptom of narcolepsy. The testicular atrophy is believed to be secondary to degenerative alterations described in the anterior pituitary lobe.

CYCLIC MANIFESTATIONS IN THE SLEEP CURVES OF PSYCHOTIC PATIENTS

CURT P. RICHTER, PH.D., BALTIMORE

Stiefler,[1] in 1926, described the case of a man, aged 39, who had survived an eight-day attack of encephalitis epidemica and under treatment had made an almost complete recovery, when suddenly he began having periods of great restlessness and wakefulness lasting for two or three days, alternating with equal periods of sleepiness and general sluggishness. Stiefler thought that this peculiar cyclic change every fifth or sixth day might be related in some way to the pathologic condition of inverted sleep (Pfaundler[2]), usually found in encephalitis and shown at one time by this patient.

Campbell,[3] in 1927, called attention to a youth, aged 19, who also had suffered from encephalitis and showed a regular six-day cycle in sleep and general behavior. Every two or three days for a year preceding Campbell's report this youth had fallen into a deep sleep from which he usually could not be aroused; this was followed by a period of equal length during which, in contrast to Stiefler's patient, the overt activity was normal. Marked fluctuations in pulse rate and body temperature were also observed. The pulse rate varied from 40 per minute in the sleep periods to from 120 to 140 in the normal periods; the body temperature was from 36 to 36.4 C. (from 96.8 to 97.5 F.) in the sleep periods and from 37.2 to 37.4 C. (from 98.9 to 99.3 F.) in the free intervals. During the sleep phase the patient took no food, had no bladder or bowel movements, and assumed peculiar postures.

It seems surprising that such a regular rhythm in sleep and general behavior has not been observed many times before. That it must occur fairly frequently is shown by the fact that in a review of several hundred case histories from the Phipps Psychiatric Clinic, three patients were found who showed a similar sleep cycle during their stay in the hospital.

REPORT OF CASES

CASE 1.—E. R., a woman, aged 30, whose condition was diagnosed as "constitutional inferiority with hypomanic features," had shown regular cycles of three or four excited days followed by one or two sluggish days for a period of twelve months, three of which were spent in the clinic. The cyclic changes can be seen clearly in the chart (*C*) in which the sleep in hours is indicated by the ordinates and the time in days by the abscissas. The hours of sleep vary from three to nine during the two phases. This patient gave no history of encephalitis. She had purpura haemorrhagica at the age of 10, after which she had shown marked

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From the Psychobiological Laboratory, Phipps Psychiatric Clinic, Johns Hopkins Hospital.

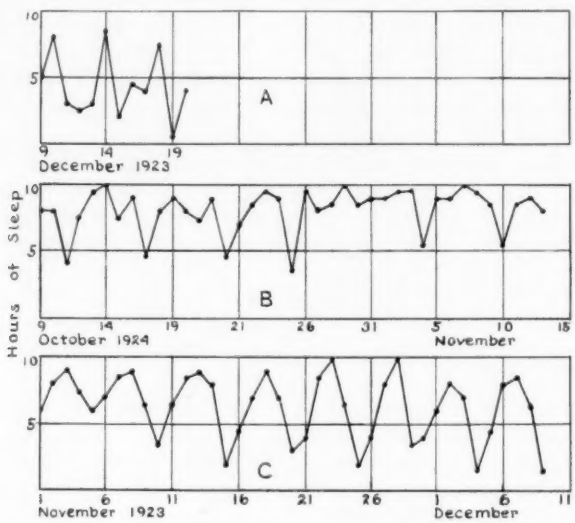
1. Stiefler, G.: Circular Disturbances of Sleep After Lethargic Encephalitis, München. med. Wchnschr. **73**:981, 1926.

2. von Pfaundler: München. med. Wchnschr. **67**:885, 1920.

3. Campbell, D.: Periodische Schlafzustände nach Encephalitis epidemica, Monatschr. f. Psychiat. u. Neurol. **65**:58 (June) 1927.

seasonal variations in general activity and mood, being very active in the spring and very sluggish during the fall and winter months. Four years before the onset of the regular cycles described, she had influenza and pneumonia, which seemed to accentuate all the seasonal swings of mood. Menstruation had started at 11, was always profuse and prolonged, and recurred at short intervals. Masculine hair distribution, in conjunction with this abnormal menstrual function, suggested a glandular involvement.

Case 2.—E. B., a girl, aged 21, whose condition was diagnosed as "schizophrenia with hypomanic features," presented cyclic changes in sleep with a duration of from five to seven days; they were much less regular than in case 1. The sleep record is presented in the chart (*B*). This patient had frequent attacks of moodiness and depression which were pronounced during menstruation. She had frac-



Sleep curves of three patients whose conditions were diagnosed, respectively, as (*A*) senile paranoia with trancelike states, (*B*) schizophrenia with hypomanic features and (*C*) a constitutional inferiority with hypomanic features.

tured several cervical vertebrae the year before the onset, while diving into shallow water, but showed no other physical injuries. There was no history of encephalitis or of influenza. A glandular involvement in this case is suggested by the fact that the patient gained weight so rapidly after she left the clinic that in a short time she was almost unrecognizable.

Case 3.—E. G., a man, aged 57, whose condition was diagnosed as "senile paranoia with trancelike states," was admitted to the hospital in a stuporous condition. He emerged from this in two days, but showed cyclic trancelike states accompanied by marked gastro-intestinal disturbances during the eleven days he stayed in the clinic. On his sleep curve, presented in *A* in the chart, the five-day cycles can be clearly seen. There was no history of encephalitis or of glandular disturbances.

The apparent rarity of observations of cyclic changes in sleep may be due in large part to the action of hypnotics which tend to obliterate rhythms of any sort. The appearance of cycles in the patients whose cases are reported may be attributed to the fact that none of them was treated with hypnotics.

COMMENT

From experience in the study of cyclic manifestations in animals, I believe that the underlying factors in all these cases, in the three reported as well as in the two described by Stiefler and Campbell, is a glandular change, probably in the hypophysis (Richter [4]).

In experiments with rats it has been found that several definite cycles in spontaneous activity can be produced by manipulation of the various glands of internal secretion. Thus, castration elicits cycles of eight days; section of the pituitary stalk, cycles of from nine to eighteen days; removal of the thyroid gland, cycles of from twenty-five to thirty-five days, and removal of all but one small remnant of ovarian tissue, cycles of from ninety to a hundred and twenty days (Richter [5]). Since in all these patients there was a disturbance of sleep, the mechanism for the regulation of which is thought to be in the floor of the third ventricle, in close proximity to the hypophysis, it would seem likely that in some way this gland was injured in every case. With these facts in mind more careful future observations of patients showing cycles of from four to six days in sleep may bring out the origin of these cyclic phenomena.

SUMMARY

1. The cases of three patients are described in which sleep was characterized by regular cyclic fluctuations with a frequency of from four to six days. The condition in these three cases was diagnosed, respectively, as constitutional inferiority with hypomanic features, schizophrenia with hypomanic features and senile paranoia with trancelike states.

2. The same frequency in sleep curves was reported by Stiefler and Campbell in two patients with a history of encephalitis. Campbell's patient showed cyclic changes in pulse rate and body temperature as well.

3. It is suggested by analogy from cyclic changes observed in animals that the cycles in all of these patients may be attributed to a pathologic condition of the pituitary gland.

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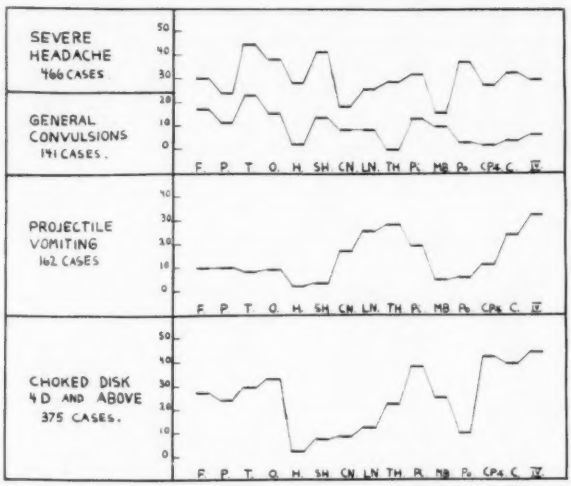
4. Richter, C. P.: The Biological Foundation of Personality Differences, Am. J. Orthopsychiat. **2**:345 (Oct.) 1932.

5. Richter, C. P.: The Rôle Played by the Thyroid Gland in Production of Gross Body Activity, Endocrinology **17**:73 (Jan.-Feb.) 1933.

FREQUENCY WITH WHICH TUMORS IN VARIOUS PARTS OF THE BRAIN PRODUCE SEVERE HEADACHE

FREDERIC A. GIBBS, M.D., BOSTON

In a recent report on the frequency with which tumors in various parts of the brain produce certain symptoms,[1] I pointed out some inconsistencies in the assumption that a considerable number of symptoms are due to increased intracranial pressure. Further study of the material (1,545 verified cases of tumor of the brain) has afforded information as to the percentage incidence of severe headache in cases of variously located tumors (chart). Headache is a symptom which, like projectile


SEVERE HEADACHE 466 CASES
GENERAL CONVULSIONS 191 CASES.
PROJECTILE VOMITING 162 CASES
CHOKED DISK 4 D AND ABOVE 375 CASES.
F. P. T. O. H. SH. CN. LN. TH. PI. MB. Po. CPs. C. IV.

Frequency with which tumors in various parts of the brain produced severe headache and certain other symptoms, generally supposed to be caused by increased intracranial pressure: *F.*, frontal; *P.*, parietal; *T.*, temporal; *O.*, occipital; *H.*, hypophysis; *SH.*, suprahypophyseal; *C.N.*, caudate nucleus; *LN.*, lenticular nucleus *TH.*, thalamus; *PI.*, pineal; *MB.*, midbrain; *PO.*, pons; *CP.*, cerebellopontile angle; *C.*, cerebellum; *IV*, fourth ventricle. The curves for severe headache and generalized convulsions are superimposed to show their similarity; the upper one is the curve for severe headache. In this curve, for example, the line at 30 over *F* indicates that 30 per cent of all patients with tumor tissue in the frontal lobe had severe headaches. Continuing on this curve, the line at 25 over *P* indicates that 25 per cent of all patients with tumor tissue in the parietal lobe had severe headaches.

From the Department of Neuropathology, Harvard Medical School and the Neurological Unit, Boston City Hospital.

1. Gibbs, F. A.: Frequency with Which Tumors in Various Parts of the Brain Produce Certain Symptoms, Arch. Neurol. & Psychiat. **28**:969 (Nov.) 1932.

vomiting, generalized convulsions and choked disk, is generally supposed to be produced by increased intracranial pressure in cases of intracranial tumor. The difference in the curves for percentage incidence of these symptoms shows that they cannot all be produced by an identical mechanism.

The curve for severe headache resembles more nearly the curve for generalized convulsions than any other symptom studied.[1] This similarity is particularly interesting in view of the relationship supposed to exist between epilepsy and migraine. Moreover, the patients frequently reported that the pain was unilateral and that it disappeared after an attack of vomiting. It is possible that there is more than an analogy between the headache produced by expanding intracranial lesions and migraine.

The mechanism by which tumors of the brain produce headache is obscure, but whatever the mechanism, the neural elements involved appear to be more diffusely distributed than those concerned in the production of other symptoms. The chart indicates that the symptoms have particular relation to the temporal lobe, the suprahypophyseal region and the pons. One cannot help wondering whether this is because the neural elements concerned are distributed, as has been suggested, along the cerebral arteries, and are, therefore, concentrated at the base of the brain.

STANDARDIZATION OF THE LANGE TEST

Control of Buffer Value and Colloidal Quality of Gold Sol with the Use of Secondary Sodium Phosphate

WINIFRED ASHBY, PH.D., WASHINGTON, D. C.

The Lange colloidal gold test is to date a purely empirical test since its mechanism is not yet understood. It has been explained on the assumption that the precipitation of the gold sol is due to the discharge of its negatively charged particles by the positively charged protein ions of the spinal fluid. These positively charged ions are so charged because the proteins from which they are derived are on the acid side of their iso-electric point. This of course presupposes that in a spinal fluid with a positive reaction there is a protein that is on the acid side of its iso-electric point at the p_H to which the colloidal gold is adjusted in the Lange test. This conception includes the possibility that there may be present proteins which are on the basic side of their iso-electric point and which, if effective, act as protective substances. The hypothesis probably represents the facts, but more work should be done in the line of analyzing the proteins of the spinal fluid with reference to their iso-electric points. Such work may, I think, retrieve the Lange test from the field of empiricism.

In the meantime the hypothesis is useful and must be taken into consideration when adjusting the Lange test. For instance, if the 0.2 cc. of spinal fluid used in the test is diluted in the usual way with 0.4 per cent saline solution, a gradient of alkalinity is established through the ten tubes owing to the buffer value of the alkaline spinal fluid, which gradient is maintained even after the addition of the 5 cc. of colloidal gold. This gradient of p_H, plus the gradient of increased dilution of the spinal fluid, is undoubtedly responsible for the physical distinction between the three zones of the test which produces the dementia paralytica, the syphilitic and the meningitic types of precipitation, respectively. These points were worked out by Shaffer [1] at the Mayo Clinic and by Wright and Kermack [2] in Edinburgh.

It is important, therefore, that this gradient of p_H, which is established by the considerable buffer value of the alkaline spinal fluid, shall not be destroyed, and in consequence it is necessary that the buffer value of the gold added to the much smaller amount of spinal fluid shall not be such as to destroy this gradient. In the method of making colloidal gold which I have worked out for St. Elizabeth's Hospital and which I shall describe, this relationship between the buffer value of the spinal fluid and the buffer value of the colloidal gold is controlled by making the colloidal gold with secondary sodium phosphate in place of potassium carbonate. The advantage of the use of the stable phosphate salt in place of the carbonate, which is volatile in the presence of acids, is obvious in this connection. In the laboratory of St. Elizabeth's Hospital oxalate has been adopted as the reducing

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From St. Elizabeth's Hospital.

Read at a meeting of the Section of Nervous and Mental Diseases of the Medical Society of the District of Columbia, Jan. 2, 1933.

1. Shaffer, L. W.: The Effect of Hydrogen-Ion Concentration on the Precipitation of Colloidal Benzoin and Gold Solutions by Cerebrospinal Fluid, J. Lab. & Clin. Med. **9**:757 (Aug.) 1924.

2. Wright, H. D., and Kermack, W. O.: The Mechanism of Precipitation of Colloidal Gum Benzoin by Cerebrospinal Fluid, Biochem. J. **17**:658, 1923.

agent; it is used as in the Mellanby and Anwyl-Davis technic, rather than formaldehyde or dextrose; with the minimal amounts of oxalate used, the oxalate practically all disappears as carbon dioxide, while formaldehyde and dextrose, the other two reducing agents commonly used in making colloidal gold for the Lange test, are likely to leave an indefinite residue of potential buffer substances, such as formic acid from the oxidation of formaldehyde or oxycarboxylic acid from the oxidation of dextrose.

With the buffer value under control it becomes of interest to see what the margin of safety is in the use of secondary sodium phosphate as an alkalinizing agent in making colloidal gold. In table 1 are given the resultants of the buffer value of the alkaline spinal fluid and the buffer value of acidified secondary sodium phosphate, p_H 6.2 and p_H 6.4, in the three dilutions, 0.01, 0.02 and 0.45 per cent. Spinal fluids with positive and with negative reactions were used; the amounts of spinal fluid taken were equal to those of the first three tubes of the Lange test, the dilutions being made in the usual way. As will be seen, a definite increase

TABLE 1.—*Gradient of p_H: Resultant of Buffer Value of Spinal Fluid Used in the First Three Tubes of the Lange Test and the Buffer Value Equivalent to 5 Cubic Centimeters of Gold Sol Made with 0.01, 0.018 and 0.045 Per Cent Secondary Sodium Phosphate, Adjusted to p_H 6.4 and p_H 6.2*

	Secondary Sodium Phosphate					
	0.01 per Cent		0.018 per Cent		0.045 per Cent	
Spinal Fluid (Negative)	p_H	p_H	p_H	p_H	p_H	p_H
0.1 cc.	7.2	7.1	7.0	6.9	6.6	6.7
0.05 cc.	6.9	6.9	6.7	6.6	6.6	6.7
0.025 cc.	6.7	6.6	6.5	6.5	6.5	6.5
0 cc.	6.4	6.2	6.4	6.2	6.4	6.2
(Dementia Paralytica)						
0.1 cc.	7.2	7.0	6.9	6.8	6.7	6.6
0.05 cc.	6.9	6.8	6.8	6.7	6.6	6.4
0.25 cc	6.9	6.7	6.7	6.5	6.5	6.4
0 cc.	6.4	6.2	6.4	6.2	6.4	6.2

in p_H was maintained by the spinal fluid, even against the highest percentage of phosphate; it would seem, then, that 0.015 per cent, which I regularly use in making gold sol, is well within the limits of safety.

On the other hand, there is the possibility of the colloidal gold having too little buffer value. With a spinal fluid that has stood for some time, with loss of carbon dioxide and a consequent development of a high degree of alkalinity, the p_H of the first tubes of the Lange test may be so high that it is near to or beyond the iso-electric point of the proteins that are effective in the positive spinal fluid. In that case there would not be produced a sufficient number of positively charged protein ions to cause precipitation by discharging the negatively charged colloidal gold. The following is such an instance:

> Lange test on the positive spinal fluid of a patient with dementia paralytica, run with an acid colloidal gold of low buffer value:
>
> Lange test 145,554,321
>
> Buffer value of colloidal gold adjusted by addition of 0.01 per cent secondary sodium phosphate and acidity decreased to p_H 6.2:
>
> Lange test 555,554,321

The colloidal gold, tested with the known positive spinal fluid of a patient with dementia paralytica, was made by a method which gave practically no buffer value to the finished product. The first test, although run with a highly acid gold preparation, beyond the range of bromcresol green, gave incomplete precipitation in the first tubes; after increase of the buffer value by the addition of 0.01 per cent secondary sodium phosphate and adjustment of the p_H to 6.2, the typical curve of dementia paralytica was obtained.

The degree of acidity to which the colloidal gold is adjusted before use in the Lange test is of importance. If consistent results are desired, the same degree of acidity should be maintained in a given laboratory by titrating the gold sol prior to use. The original technic of Lange called for a gold sol neutral to alizarin red, the end-point being chosen (a sherry color) on the acid side of neutrality. Various degrees of acidity have been recommended, ranging from p_H 6.1 to 6.2 to as high as from p_H 7.1 to 7.2. In the hospital laboratory the gold sol is titrated on the day it is used against a buffered standard of bromcresol purple to a p_H from 6.2 to 6.4. Bromcresol purple is a satisfactory indicator to use for this purpose because in this range it makes a sharp color change that the gold sol

TABLE 2.—*Effect on the Lange Test of p_H 6.4, p_H 6.0 and p_H 5.6 with a Buffer Value Due to 0.02 Per Cent Secondary Sodium Phosphate*

	p_H of Gold	p_H of Mixtures of Phosphate and Spinal Fluid Equivalent to First Three Tubes of Test	Lange Test
Spinal fluid from active case of dementia paralytica	6.4	6.9, 6.7, 6.7	555,554,321
	6.0	6.7, 6.5, 6.5	555,555,422
	5.6	6.6, 6.4, 6.4	555,555,432
Spinal fluid giving precipitation in the middle zone	6.4	6.9, 6.7, 6.7	112,233,000
	6.0	6.7, 6.4, 6.4	222,333,210
	5.6	6.5, 6.4, 6.4	122,333,210
Fluid of patient treated for dementia paralytica	6.4	6.9, 6.7, 6.6	333,332,210
	6.0	6.7, 6.5, 6.5	444,442,210
	5.6	6.7, 6.6, 6.5	555,554,422

does not mask. The effect of the use of the more acid colloidal gold is to increase sensitiveness, but I do not believe that it affects whatever specificity the Lange test may have, provided the presence of hemoglobin is ruled out. In questionable cases this is done with the benzidine test. In table 2 is given the result of a representative test to determine the effect of the three degrees of acidity, p_H 6.4, p_H 6.0 and p_H 5.6, using the buffer effect of 0.02 per cent secondary sodium phosphate, which is slightly in excess of that used in the routine test. The three spinal fluids chosen were: a fluid from an active case of dementia paralytica, a fluid from a patient treated for dementia paralytica and a fluid which gave precipitation in the middle zone. The gradients of alkalinity of the first three tubes under these degrees of acidity are also given in table 2. The effect of increase in acidity on the curve of the fluid from the active case of dementia paralytica was slight; the fluid from the treated patient was definitely increased in positiveness; the fluid with middle zone precipitation was practically unchanged.

By far the biggest factor in determining the usableness of colloidal gold for the Lange test is the degree of dispersion of the sol. A very coarse suspension is precipitated by a negative spinal fluid even at a neutral or slightly alkaline reaction. On the other hand, sols can be made of such a high degree of dispersion that they have the appearance of crystalline solutions; these sols are not adequately precipitated by spinal fluids even when they are well on the acid side of neutrality.

Mixtures of two such sols are wholly unsatisfactory because they give incomplete precipitation in the first tubes of a positive fluid from a patient with dementia paralytica and carry the precipitation too far down in the last tubes. A mixture composed of a sol which gives complete precipitation in two or three tubes and a sol which is too sensitive may work sometimes, but, on the whole, mixtures of sols are to be deprecated.

With any well tried method of making colloidal gold the important factor is the quality of the distilled water. With some runs of water it is impossible to make a fine-grained colloidal gold by any method, while with other specimens of distilled water a colloidal gold of such great dispersion may result that it is too insensitive to use in the Lange test. A good deal has been written about the water for colloidal gold, especially during the last year. Zsigmondy, who was the pioneer in the study of colloidal gold and who chose colloidal gold for the subject of his Nobel prize address, stipulated that the water used in making colloidal gold should be distilled water redistilled from a silver still into non-sol glass. He believed that a certain amount of particulate matter was probably necessary for formation of nuclei which determined the dispersion of the colloidal gold. Other workers, among them von Weimarn,[3] believe that the water should be of absolute purity and that the dispersion of the sol depends on nuclei which are formed by insoluble intermediate products of reduction such as gold hydroxide. Recently, Wernicke and Modern[4] reported that water electrodialyzed through parchment paper or cellophane is suitable for the preparation of colloidal gold, while water dialyzed through collodion is not; Levine[5] has repeated these results and has discussed other factors. Wernicke and Lossen[6] claimed that contact with rubber makes water suitable for the preparation of gold sol.

I, myself, am convinced that it is impurities in the water that are responsible for suppression of formation of nuclei and that lead to the formation of coarse sols. I am of the opinion that these impurities are probably organic. For many years gold was made by my phosphate method, and I attributed the 100 per cent success to the method. At the time the water used came from the hospital's artesian wells. The water was sterile and probably free from all organic impurities; it was distilled in the ordinary laboratory still. In the course of time the pumping system became inadequate, and water was bought from the city. Then trouble developed with the colloidal gold; this was at first blamed on the still, but with the installation of a triple still run from condensation of steam from the engine room troubles multiplied. It was found that the pipe connections carrying the steam were greased, and undoubtedly a certain amount of volatile oil was carried over with the steam, as a film of oil could often be seen on the surface of this water. Double and triple distillation of the water from an non-sol glass still was resorted to, sometimes with unfavorable results. As the still stood in the sunlight and as, at times, the efficiency of the water was recovered by prolonged

3. von Weimarn, P. P.: Studies of the Dispersoid Synthesis of Gold: I, Kolloid Ztschr. **33**:228, 1923.

4. Wernicke, R., and Modern, F.: Colloidal Gold for Use in Lange's Reaction: Use of Electrodialized Water in Preparation of Gold Sol, An. Asoc. quim. argent. **16**:247, 1928.

5. Levine, B. S.: Making Colloidal Gold, Am. J. Syph. **16**:103, 1932.

6. Wernicke, R., and Lossen, R. B.: Preparation of Gold Sols by Zsigmondy's Method: Influence of Distilled Water. Action of Traces of Hydrogen Sulphide, An. Asoc. quim. argent. **6**:321, 1930.

boiling, I thought it possible that on sunny days peroxide might be produced in a small amount. When this water was used in making colloidal gold, the peroxide might reduce the gold salt more readily than the potassium oxalate-producing nuclei, on which the gold resulting from reduction by potassium oxalate would be deposited, thus producing coarse-grained colloidal gold. This, however, did not prove a serviceable lead, and I am of the opinion that whatever improvement occurred in the water from boiling was due to the removal of volatile substances. In this vicinity the water comes from the Potomac River which in the summer is heavily overgrown with weeds and in which fish are plentiful. It is extremely probable that it contains minute quantities of volatile oils produced from fish and decayed weeds. Oils, according to Freudlich,[7] inhibit the formation of nuclei in gold sols. I now use permanganate to oxidize any organic matter present, and further I use a silicate dust, instead of glass beads or broken glass, to reduce thumping, for, according to my experience, there is a great deal more carrying over of spray during distillation than is usually assumed to be the case. The water is distilled twice. Since this procedure has been adopted the water obtained has uniformly given highly dispersed colloidal gold.

With the increase in purity of the water, however, such highly dispersed gold has resulted that it was unsuitable for the Lange test. It has become a problem to produce gold of uniform texture with particles sufficiently large for sensitiveness.

An attempt was made to increase sensitiveness in three different ways. First, I tried increasing the amount of reducing agent. The rationale for this procedure came out of some experimental work which was part of a series of investigations on colloidal gold to be published elsewhere, and of which the procedures developed in this paper are the practical outcome. With certain runs of water this modification of the formula used was successful, but with others so much reducing agent had to be added before the necessary degree of sensitiveness was secured that danger arose of overloading the buffer system. Another device introduced by my associate, Miss Tice, was successful; it consisted of mixing a very pure water with water of a lower degree of purity and of making gold sol from the mixture. This method, although it could be made to work, introduced a large amount of chance and with it waste of time and material. I therefore introduced a method which I call the pyramiding method. It consists, first, of a modification of the Mellanby and Anwyl-Davis technic, in which secondary sodium phosphate is used in place of the potassium carbonate or sodium hydroxide already in use. Then, if the gold is too clear, as it usually is, the colloidal gold is taken in place of water and the whole process is repeated. This is done again and again without dilution until colloidal gold is obtained that has particles sufficiently large to be sensitive. A very little experience enables one to see when this point is reached by the appearance of the colloidal gold in reflected light. It is sometimes necessary to pyramid eight or ten times. The sol is then diluted with ordinary distilled water until it contains the standard amount of gold per liter.

The colloidal gold after adjustment to a p_H from 6.2 to 6.4 is tested with a 1:400 dilution of blood from a healthy man. The blood is taken as for a red cell count, but water is used as the diluent. After being well shaken, the contents of the pipet are expelled into a small tube and, with the same pipet, an equal amount of physiologic solution of sodium chloride is added. This hemoglobin dilution is then run through a series of dilutions as though it were a spinal fluid. It is

7. Freudlich, H.: Colloid and Capillary Chemistry, New York, E. D. Dutton & Co., Inc., 1926, p. 501.

required that the first four tubes and only these shall completely precipitate the gold sol. As a fact, with hemoglobin the change preceding precipitation is rather sharp and rapid, so that soon after making the test one can predict what the reading on the next day will be; if the colloidal gold is not sufficiently sensitive, the pyramiding is repeated.

This hemoglobin check on the sensitiveness of colloidal gold has been used in the hospital laboratory for several years. In the meantime the use of hemoglobin in a slightly different manner has been advocated by Patterson[8] of London. As a result of considerable experience with the titration of hemoglobin I can vouch for its efficiency with acid gold sol at a p_H of from 6.2 to 6.4, but I do not consider it a satisfactory indicator if a gold of from p_H 6.8 to 7.0 is to be used. Cleancut results are not obtained at a point so close to neutrality, which is what one would expect, since the iso-electric point of oxyhemoglobin is approximately p_H 6.8. Ellisch and Einstein[9] have recommended the use of glycine for the standardization of colloidal gold, and Kreidler and Small[10] have recommended the use of edestin. According to Rona and Michaelis,[11] the iso-electric point of edestin is 1.3×10^{-7} or approximately p_H 6.9; the efficiency of edestin should therefore be about equal to that of hemoglobin. According to Hiraki,[12] the iso-electric point of glycine is near to p_H 6.1; in order to use glycine as an indicator of sensitiveness, the gold sol would have to be used well on the acid side of p_H 6.0. Of course, the ideal protein for use in titrating colloidal gold for the Lange test would be one with an iso-electric point equal to that of the protein responsible for the positive curve of dementia paralytica, which must be p_H 7.6 or more. I do not consider dilutions of salt a satisfactory means of titrating colloidal gold because the effect of salt, within the ranges under consideration, is independent of acidity, whereas the sensitiveness of colloidal gold to a positive spinal fluid depends both on its acidity and on its degree of dispersion.

I prefer to use a set p_H and adjust the colloidal quality of the gold to produce a fixed degree of sensitiveness to a standard, rather than to adjust the sensitiveness by means of variation in acidity as is recommended by the authors who propose the use of hemoglobin, edestin and glycine as indicators. The adjustment which these authors recommend would be theoretically correct only if one were testing spinal fluid for the protein used as the standard or for a protein whose iso-electric point was close to that of the test protein. The adjustments of acidity which would counterbalance the effects of variation in size of the gold particle of any two gold sols against precipitation by a protein whose iso-electric point was at one p_H would not necessarily produce proportionate adjustments to another protein whose iso-electric point was at a decidedly different p_H. There is no reason to assume that the protein which produces the positive curve of dementia paralytica has an iso-electric point very near to that of any of these proteins proposed as standards, as precipitation of gold sol may be produced by a strongly positive

8. Patterson, J.: Gold Preparation and Standardization for the Lange Test, Brit. J. Exper. Path. **12**:143, 1931.

9. Ellisch, G., and Einstein, O.: Standardization of Gold Sol for the Lange Gold Sol Reaction, Naturwissenschaften **19**:506, 1931.

10. Kreidler, W. A., and Small, J. C.: Method of Standardization of Colloidal Gold Sol, J. Lab. & Clin. Med. **17**:259, 1931.

11. Rona, P., and Michaelis, L.: Biochem. Ztschr. **28**:193, 1910.

12. Hiraki, M.: Isoelectric Point of Glycine and Alanine, J. Biochem. **15**:345, 1932.

fluid from a case of dementia paralytica at a degree of alkalinity at which any of these proteins would have a protective effect. One is therefore not justified, at least from the theoretical standpoint, in using them to produce standard gold unless the golds tested with the protein standard are tested at a fixed p_H.

As a result of these various considerations it is the routine in the hospital laboratory: (1) to control the buffer value of colloidal gold by the use of 0.015 per cent of secondary sodium phosphate ($Na_2HPO_4.12H_2O$ [M. $4\frac{2}{100.000}$]) in place of the usual alkalinizing substances, and by the use of potassium oxalate, which in minimal amounts disappears as carbon dioxide, for the reducing substance; (2) to control the dispersion of the gold by pyramiding; (3) to titrate to p_H from 6.2 to 6.4 on the day the gold is being used. Three checks are made with each set of spinal fluids tested, including the known positive, which is required to check closely with the result previously obtained with the same fluid, and the known negative; in addition, in order to stabilize the results over a long period it is required that the gold shall be precipitated in the first four tubes and only in the first four tubes by a 1:400 dilution of blood having a hemoglobin content equivalent to that of a healthy man, the hemoglobin dilution being used as a spinal fluid.

SUMMARY

The procedure for the Lange test as used at St. Elizabeth's Hospital, the federal hospital for mental and nervous diseases, is described.

The importance of purity of the distilled water used in making the gold sol is stressed, and the possibility of volatile oils as a factor in unsatisfactory water is considered.

Protein tests for sensitiveness are discussed.

The factor of the relative buffer value of the alkaline spinal fluid and the acid colloidal gold, hitherto not considered in the Lange test, is recognized and controlled by the use of secondary sodium phosphate and potassium oxalate in the process of making the gold sol.

A method of controlling the sensitiveness of the gold sol by pyramiding, a procedure to be discussed in greater detail elsewhere, is briefly described.

REFLEXES IN AMYOTONIA CONGENITA (OPPENHEIM)

Report of a Case with Signs of Involvement of the Pyramidal Tract

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The following case of amyotonia congenita is of interest because of the unusual presence of signs of involvement of the pyramidal pathway, in contradistinction to the inevitable findings of absence of the deep reflexes.

REPORT OF CASE

History.—The patient, M. M., was a white girl, aged 2½ years; the father, aged 40, the mother, aged 32, a sister, aged 8 years, and a brother, aged 6 years, were all in normal health. No pathologic familial traits were known to exist The child was born at term; the delivery was normal, and the weight at birth was 8½ pounds (3,855.6 Gm.). She had no illnesses other than the present condition. At 4 months it was noted that she was not like other children. Her cry was feeble; she gained weight slowly, and she could not move her legs. As she grew older, she began to show symptoms of a definite muscular disorder.

Examination.—A general medical examination gave negative results. Neurologically, there was good vision; the response of the pupils to light and in accommodation was prompt; the extrinsic muscles of the eyes and the eyegrounds were normal. The hearing was good. The face had a dull, passive expression; the child could smile, but feebly. Articulation was limited to a few words. The mouth was relaxed, and there was some drooling. The movements of the tongue and the acts of swallowing and chewing were normal.

The head fell forward on the chest if unsupported, because of a marked hypotonicity of the muscles of the neck, and, owing to inability to hold up the back, the body slouched forward in a kyphotic attitude. The child could not sit or stand alone, and if placed erect on her feet slumped to the ground in a heap. The upper and lower extremities were hypotonic. The hand grasp was weak, but she could hold light objects and could feed herself. Both upper extremities had a limited range of voluntary motion. She moved the legs but little. She could flex the right thigh on the abdomen, but there was scarcely any perceptible motion in the left lower extremity. All the muscles were soft and flabby. There was no atrophy, hypertrophy, contractures or abnormal movements.

The skin was hypesthetic throughout to pin-prick. Sphincteric control was normal. Mentally the child was retarded, although she seemed observant and obeyed a few simple commands.

The abdominal reflexes could not be obtained. The conjunctival and pharyngeal reflexes were present. Wrist, biceps, triceps, patellar and achilles reflexes were decidedly exaggerated, equally on both sides. There was bilateral fanning of the toes on plantar stimulation, with a suggestion of Babinski responses, which was also obtained with the Gordon and Oppenheim maneuvers. There was a pronounced ankle clonus on the left, with a somewhat lessened response on the right.

The Wassermann examination of the blood gave negative results. The weight at the time of examination was 22 pounds (9,979.2 Gm.).

COMMENT

Oppenheim [1] described this disease in 1900 as one in which "there is a striking flaccidity of the muscles of the lower, sometimes also of the upper, limbs, much less often of those of the trunk. The limbs may be moved like loose appendages. The tendon reflexes are weakened or lost. . . . Active movements are feeble; the child appears paralyzed, yet on closer examination one recognizes that in most cases a certain amount of power of movement is present." Since then, amyotonia congenita has always been described as a condition of extreme flaccidity of the muscles associated with complete or partial loss of the deep reflexes.

Collier and Wilson [2] considered that the sphincters are never affected, that the superficial reflexes are always natural, and that the deep reflexes are invariably lost in the regions in which the amyotonia is most marked. It seems highly probable, they added, that the deep reflexes are always absent from the start, and that with the improvement in the status of the muscles the deep reflexes tend to return. They tabulated the clinical findings in 25 cases reported in the literature, including several of their own. The knee jerks were absent in 22. The wrist and elbow jerks were absent in 15 and present in 4. In one case the knee jerks returned after five years of improvement, and in another, after nine months.

In Faber's [3] summary from the literature the knee jerks were tested in 94 cases; they were absent in 69, diminished in 17, present, though the degree was not noted, in 15, and normal in 2. The superficial reflexes were present in 20 instances and absent in 20. The Babinski, Oppenheim and Gordon signs occurred a few times, but nearly always before the walking age; they therefore were of questionable significance. Faber, postulating a congenital defect in the lower motor neuron, said that the deep reflexes were present in 26.6 per cent of all the cases on record.

Reuben [4] reported on 130 cases from the literature, adding several of his own. In almost all the superficial reflexes were not tested, but in 60 per cent of those in which they were examined they were normal. The deep reflexes were entirely abolished in 84 cases, present feebly in 21, and normal or nearly so in 13. The Babinski sign was positive 4 times. In a few instances the conjunctival and pharyngeal reflexes were absent. There was no conformity between the deep and the superficial reflexes. As a rule, the knee jerks were most uniformly absent and the superficial reflexes uniformly present. The deep reflexes may be present in the upper extremities and absent in the lower ones, and vice versa; they may be diminished in one part of the body and normal in another. In 6 cases the knee jerks appeared after having been completely absent from birth. In not a single case did they disappear after once appearing.

Haberman [5] referred to a study made at Hagenbach's clinic at Basel, which demonstrated that the reflexes are always absent in this disease. He summarized 36 cases from the literature. In all the patellar reflexes were absent; in some

1. Oppenheim, quoted by: Greenfield, J. G., and Stern, R. O.: Brain **50**:652, 1927.

2. Collier, J., and Wilson, S. A. K.: Brain **31**:1, 1908.

3. Faber, H. K.: Amyotonia Congenita: A Survey of the Known Cases with a Report of Three New Cases, Am. J. Dis. Child. **13**:305 (April) 1917.

4. Reuben, M. S.: Amyotonia Congenita of Oppenheim, Arch. Int. Med. **20**: 657 (Nov.) 1917.

5. Haberman, J. V.: Am. J. M. Sc. **139**:383, 1910.

the skin reflexes were also lacking. He concluded that, as a general rule, the deep reflexes are either much weakened or abolished. According to Pearce,[6] the tendon reflexes vary with the degree of myotonia present. In the opinion of every writer on the subject the deep reflexes are abolished or diminished. The following collective summary of all available reports shows this to be true with but a few exceptions:

Reflexes as Reported	Number of Cases
All deep reflexes abolished	82
All deep reflexes weak	23
All deep and superficial reflexes abolished	2
All deep and superficial reflexes weak	1
All deep reflexes obtained only at intervals	1
All deep reflexes abolished; superficial reflexes present	7
All deep reflexes abolished; superficial reflexes weak	1
All deep reflexes weak; abdominal reflexes present	1
All deep reflexes abolished; upper abdominal reflexes present, lower reflexes absent	1
All deep reflexes, except plantar, abolished	5
All deep reflexes abolished, but Babinski sign present	4
Deep reflexes present in lower extremities; absent in upper	2
Deep reflexes absent in lower extremities; present in upper	1
Knee jerks and wrist jerks present, triceps jerks absent	1
Knee jerks absent	2
Knee jerks weak	1
Knee jerks absent, other deep reflexes and superficial reflexes present	1
Knee jerks weak; plantar reflexes normal	1
Knee and ankle jerks weak	1
All deep reflexes present	8
Knee jerks present	1
Babinski sign positive	1
All deep reflexes increased; abdominal reflexes absent	1
All deep reflexes increased; abdominal reflexes absent, pharyngeal and conjunctival reflexes present; bilateral ankle clonus, bilateral Babinski sign present	1
	150

In 150 cases here considered, the deep reflexes were abolished or weak in 123 instances, and present or partly present in 21. The Babinski sign was positive 5 times. In one case[7] all the deep reflexes were moderately increased, and the abdominal reflexes were absent. This case was diagnosed as one of muscular hypotonia associated with congenital heart disease.

It would seem, then, that the case reported here offers the only instance on record in which pathologic reflexes have been found in Oppenheim's disease. It manifests the paradoxical picture of generalized hypotonia associated with generalized hyperreflexia. Ankle clonus, the Babinski sign and exaggerated reflexes indicate involvement of the pyramidal tract, which should be associated with increased rather than with diminished muscular tonicity. In the absence of consistent pathologic observations in Oppenheim's disease, with its known tendency to improvement, it has been postulated that the disorder is due to a congenital physiologic delay in the development of the lower motor neuron and its constituents. It might be contended, in this case, that there is a concomitant retardation in the pyramidal tract.

6. Pearce, N. O.: Amyotonia Congenita, Am. J. Dis. Child. **20**:393 (Nov.) 1920.

7. Davidson, C., and Weiss, M. M.: Muscular Hypotonia Associated with Congenital Heart Disease, Am. J. Dis. Child. **37**:359 (Feb.) 1929.

News and Comment

CLEVELAND SESSION—AMERICAN MEDICAL ASSOCIATION

Scientific Exhibit

The Section on Nervous and Mental Diseases of the American Medical Association will sponsor a section exhibit in the Scientific Exhibit at the Cleveland Session, June 11 to 15, 1934. The section exhibit committee is composed of: Groves B. Smith, chairman, Godfrey, Ill.; Thomas J. Heldt, Detroit, and Lloyd Ziegler, Albany, N. Y.

Applications for space will close on Feb. 26, 1934. Application blanks may be obtained from the members of the committee or from the Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago.

AMERICAN ORTHOPSYCHIATRIC ASSOCIATION

The eleventh annual meeting of the American Orthopsychiatric Association will be held at the Palmer House in Chicago, Feb. 22 to 24, 1934. Dr. Phyllis Bartelme is chairman of arrangements.

Abstracts from Current Literature

BINOCULAR MOVEMENTS. ALEXANDER DUANE, Arch. Ophth. **9**:579 (April) 1933.

This article is another posthumous chapter of Dr. Alexander Duane's unpublished textbook on "A New Classification of the Motor Anomalies of the Eye Based Upon Physiological Principles, Together with Their Symptoms, Diagnosis and Treatment." The various sections which have appeared in the *Archives of Ophthalmology* in the past two years have been permitted through the courtesy of Mrs. Duane. In this discussion of binocular movements, Duane has considered in detail the various conjugate binocular movements from the standpoint of synergistic intrinsic muscles. Detailed tables are included to illustrate the muscular action in the form of the various conjugate movements.

Duane groups the movements under two varieties: versions and cycloversions. The first four are the lateroversion or movements of both eyes to either the right or the left; superversion, or movement of both eyes upward; subversion or movement of both eyes downward, and oblique movements which are combined with lateroversion and elevation or depression. He believes that these are performed as the result of an effort set up by a stimulus emanating either from the frontal or occipital cortex or from the labyrinth. He also thinks that lateroversion is primarily a stimulus derived from one side of the brain, but that its complete performance requires the cooperation of both sides, and that the up and down versions are produced by stimuli which are essentially bilateral in origin. He states that the stimuli for the lateroversions are transmitted through the posterior longitudinal bundle, and that the up and down versions are transmitted by some channel as yet unknown.

The second variety of conjugate or bilateral versions are right cycloversion, or a tilting of both vertical meridians to the right, and left cycloversion, which is the opposite. Duane thinks that in all probability the cycloversions do not demand for their production any special nervous mechanism. If so, cycloversions as they normally occur must be due to peripheral peculiarities and not to central impulses.

In this same subsection of versions and cycloversions are discussed the fields of action of the various associated muscles, the manner in which they are grouped for performing the various conjugate movements, the six diagnostic directions of the gaze in binocular vision, the limits and fields of binocular excursions and a comparison of those with the field of binocular single vision. A chart in this subsection is especially valuable for a comprehensive study of gaze. It shows how (as the eyes are directed to the various fields) the muscles effecting the movement work singly or together, both those of primary importance and those of secondary assistance as well. At the same time, the nonproductive action of all the other muscles, whether neutralized by an antagonist or wholly absent, is indicated.

The second part of this chapter considers the varieties of the vergences, i. e., movements that cause the visual lines or the vertical meridans of the two eyes to turn toward each other, or when so turned to separate again. The impulse that effects this mutual approach or separation always seems to be equal for the two eyes. The various vergences include convergence, divergence, supervergence, i. e., divergence or convergence in the vertical plane, and convergent or diverent torsions. The nature of the various vergences, their fields and their measurements are considered in detail.

Some of these subsections are so valuable and so well presented that the reviewer has included them in full.

"Relation Between Meter-Angle and the Convergence Angle.—The supposed advantage of the meter-angle is that it indicates the relation between convergence

and accommodation. Thus, a man who is exerting a convergence of 3 meter-angles —representing a convergence distance of 333 mm.—is supposedly exerting at the same time an accommodation of 3 diopters.

"As a matter of fact, the converging power so greatly exceeds the accommodating power that there is no proper relation between meter-angles and the number of diopters of accommodation that the patient is able to exert. Moreover, the meter-angle, like the convergence distance of which it is the reciprocal, gives but an approximate idea of the work done in converging, especially at very near points. The amount of this work is represented by the convergence angle, and two persons converging on a point equally remote and converging, therefore, through the same number of meter-angles will differ in the convergence angle and consequently in converging power, unless their interaxial distances are identical. Thus, 12 meter-angles may represent a convergence angle of anywhere from 19 to 22°, and 20 meter-angles a convergence angle of from 30 to 35°.

"Sherrington's Law as Applied to Divergence and Convergence; Essential Nature of These Two Functions.—There appears to me no reason to doubt that Sherrington's law, which governs both the movements of each eye separately and the conjugate movements of the two eyes, also governs convergence and divergence. If this is true, convergence consists in an equal simultaneous contraction of both interni combined with a simultaneous relaxation of both externi. Divergence would consist in exactly the reverse process.

"Furthermore, the statements regarding the varying effectiveness in action of the muscles in moving the eye first outward and then back to the midline apply also to convergence and divergence. That is, the muscles that effect either action work to the greatest advantage at the beginning of the movement and less and less advantageously as the movement proceeds. So when the eyes are diverged to their fullest extent (to or beyond parallelism) they converge most readily, and when they are converged to the extreme limit they diverge most readily. Also, as in the case of conjugate movements, the action of the main convergers (the interni) and the main divergers (the externi) is supplemented by accessory muscles, which make the variations in the movement less extreme and ensure smoothness of action."

Many ophthalmologists and neurologists do not agree with Duane that divergence and convergence have similar torsions in all details, except for the resulting position of the eyeballs due to the activity of the vergences. These objectors maintain that divergence is simply a relaxation of the interni, allowing the eyes to return to a position of rest. Observers who adopt the latter view assume that the natural position of the eyes when all the muscles are relaxed is one of slight divergence, parallelism itself requiring a certain tonic and constant contraction of the interni for its maintenance.

Duane believed that the position of perfect physiologic rest, if there is such a thing, is not one of divergence, and that in any event the lateral separation of the visual lines must be regarded, in part at least, as an active process due to the simultaneous contraction of the externi combined with an inhibition of the interni. The view that the external recti thus take an active part in the diverging process is furthered by Sherrington's experiments, which showed that an inhibition of these muscles was able to produce a moderate convergence even when all the other ocular muscles, including the internal recti, are subject to a central inhibition; so as to effect some degree of convergence, they should also be subject to a central stimulation which would effect divergence. Considering this, divergence must then have for its effect as definite a center of nervous control as does convergence, and he believed that pathologic facts also prove this. This has been a controversial point for some time; it is valuable for an authority, as was Duane, to express himself so definitely.

The entire article is a masterful dissertation on conjugate movements and is well worth reading in the original.

SPAETH, Philadelphia.

THE RESIDUAL SYNDROME OF CLOSED CRANIOCEREBRAL TRAUMATISMS: A STUDY OF FORTY-THREE OBSERVATIONS FROM THE LABYRINTHINE, OPHTHALMOLOGIC AND NEUROPSYCHIATRIC POINTS OF VIEW. J. HELSMOORTEL, JR., L. BAUWENS and L. VAN BOGAERT, Rev. d'oto-neuro-opht. **10**:581 (Sept.-Oct.) 1932.

"There is no problem in neuropsychiatric practice in which the personal equation plays a greater rôle than in the diagnostic and prognostic appreciation of the sequelae of cranial traumatisms." The two current points of view (one that the syndrome is a traumatic neurosis, the other that there is an organic basis for the symptoms) are not irreconcilable. Recent anatomic studies have shown a diffusion of microscopic lesions which involve the nerve tissues, the vessels, the hemato-encephalic barrier and the plexiform apparatus, and which resemble those observed in cases of multiple sclerosis, cerebral arteriosclerosis and epidemic encephalitis. The tissue defect is the organic nucleus around which is crystallized a series of functional disorders and psychogenic reactions.

Study of the forty-three cases, protocols of which are given, is limited to an analysis of: (1) vestibular disturbances, (2) ophthalmodynamometric changes, (3) late neuropsychiatric manifestations and (4) modifications of the cerebrospinal fluid. The vestibular examination must be complete; otherwise, an isolated perturbation may be overlooked. Attention is called to the possibility of the existence of a disturbance of the otolithic apparatus while all other labyrinthine tests yield normal results. The methods devised by Quix are used to determine the state of the otolithic function. Quix believed that alterations in the maculae play the principal rôle in the vertigo that follows cranial trauma. The first vestibular examination was made not earlier than one month after the accident, and the second after several months. Sixteen patients had disturbances of the otolithic apparatus, which was accompanied ten times by hypo-excitability and four times by hyperexcitability of the labyrinth. It is rare to find at the same time hypo-excitability or hyperexcitability to the three tests: caloric, rotatory and galvanic. Spontaneous nystagmus was the sole sign in two patients with concussion of the labyrinth. It was present in seven cases of pure vestibular hypo-excitability, in three cases of pure hyperexcitability and in one case of the mixed form. Spontaneous deviation of the arms did not always accompany the nystagmus. With the galvanic test the average threshold varied between 4 and 6 milliamperes. Patients with the higher thresholds usually had otolithic disturbances also. The Romberg test was positive in only two cases. Spontaneous nystagmus was observed in fourteen patients. The tests of Quix, the galvanic and the caloric tests, were the fundamentals of the examination, to which were added supplementary tests that were necessary to furnish an exact idea of the state of the vestibular function. The seat of the lesion is usually thought to be in the cerebral *axis*, although Alexander, in one patient, located it in the maculae and cristae. Vertigo is the most persistent symptom and is accompanied by either hyperexcitability or a normal labyrinth. The evolution of the disease is classified as follows: *A*. The vestibular and otolithic apparatus may become normal. *B*. The only disturbance persisting may be an otolithic perturbation. *C*. A hyperexcitability or a hypo-excitability, found with one test only, may be observed. *D*. Isolated hypo-excitability, with disturbance of the otolithic apparatus, exists. *E*. Isolated hyperexcitability may be found. *F*. There may be a mixture of hyperexcitability and hypo-excitability. *G*. Hyperexcitability, with the otolithic syndrome may be noted. *H*. The labyrinth may be inexcitable. Type *C* was observed especially in light degrees of concussion; type *B* is a residual syndrome of light concussion, and types *D* and *E* are residual symptoms of a moderate and grave concussion. Types *E*, *F* and *G* are syndromes of transition.

Ophthalmodynamometric observations were made in thirty-five cases. In all cases negative from the otovestibular and neurologic points of view, in four cases with a light syndrome, in one with a marked concussive syndrome and in one negative case the pressure in the central artery of the retina was normal. The pressure was increased in all the other cases, with or without fracture. Hypertension of the central artery of the retina may remain a long time, although,

rarely, it may disappear after a number of months. It was found in 69.5 per cent of the established cases examined and only once in a suspected case. True papillary stasis accompanying retinal hypertension was not observed.

In the series of cases the posttraumatic syndrome of dementia, disturbance of olfaction and the focal syndrome were rare. In general, the neurologic semiology was poor, and in a number of cases the results of neurologic examination were negative. Disturbances of tonus were frequent. Pupillary changes were present in four cases and infundibulotuberian disturbances in two. Psychic aberrations are uniformly described by the patient: headache, poor sleep, disequilibration, abnormal sensitiveness to noises, heat and alcohol, giddiness, incapacity for work and distaste for life. When the history varies considerably, a morbid psychopathologic predisposition should be suspected. In most cases the terrain is unfavorable for the development of hysteria, but the continual discussions of the degree of disability cause certain patients to seek claims for damages and to become querulous, which they consciously or unconsciously justify by superadded symptoms. Most often hysteria occurs after slight traumatisms; it develops late, and the absence of neurologic, labyrinthine, ocular and biologic disturbances contrasts with the gravity of the subjective syndrome and permits its recognition.

The pressure of the spinal fluid was raised in sixteen of the twenty-six cases in which it was examined. In forty examinations, the cytologic formula was normal in fourteen; there was hyperalbuminosis in eleven; hyperalbuminosis and a proportional hypercytosis were present in ten, and in five there was hypercytosis alone or out of proportion to the albumin percentage. Four times in seventeen estimations a relatively slight hypoglycorrhachia was observed. The number of cells diminishes rapidly, but the hyperalbuminosis persists for a long time.

In cases with a marked concussive syndrome, the vestibular types *C* and *D* were most often observed. In cases with slight neurologic syndromes, the vestibular syndromes were extremely variable. In cases with a doubtful neurologic syndrome, the appearance of the vestibular types *B* and *D* requires reservation in the diagnosis of traumatic psychosis. When the neurologic examination gave negative results, vestibular and otolithic examinations also gave negative results.

When a slight retinal hypertension existed, there was most often a pure otolithic sequela. With marked retinal hypertension there was apt to be mixed hyperexcitability and hypo-excitability of the labyrinth, representing the beginning of the syndrome of inhibition. Retinal hypertension with a normal vestibular syndrome was observed only once. In two cases with a doubtful neuropsychic syndrome, otolithic disturbances were noted.

The conclusions reached are as follows: 1. There is not necessarily a relation between the gravity of the traumatism and the gravity of the prognosis, immediate or remote. 2. The authors have frequently been surprised at the tenacity of the sequelae observed in their patients. 3. In the important cases it is often difficult to determine the degree of disability. In such cases it is necessary to wait longer than has been the custom, since late complications are not exceptional. 4. Patients should be examined a number of times, beginning with the surgical stage of the accident and with the surgeon. The family should be questioned early with regard to the heredity and psychologic constitution of the patient. 5. Neuropsychiatric, otovestibular, ocular and biologic examinations should be made and repeated at intervals. 6. Owing to the poverty of objective signs, it is important to consider carefully the advisability of encephalography as a routine method of examination.

DENNIS, Colorado Springs, Colo.

A CONTRIBUTION TO THE KNOWLEDGE OF NARCOLEPSY. R. THIELE and H. BERNHARDT, Abhandl. a. d. Neurol., No. 69, 1933.

This contribution, covering 187 pages, is of exceptional value since thorough and repeated examinations were the rule among the thirty-one cases of narcolepsy studied, many of the patients having been followed over a number of years. All the patients had been seen since 1925 in the Charité, at Berlin, where narcolepsy

was formerly an exceedingly rare disorder. A detailed account of the history, clinical findings and subsequent course in each of the thirty-one patients is followed by a comprehensive discussion of the various symptoms.

It is emphasized that the condition of the patient during the attacks of sleep corresponds in every essential detail to that during normal sleep. All but five of the patients were subject to "attacks of affective tonelessness" or cataplectic seizures, a state which Thiele and Bernhardt believe differs only in degree from the muscular weakness normally accompanying emotional excitement. In agreement with Rosenthal and others they believe further that the cataplectic attack represents a state of partial sleep in which the static and tonic functions alone are inhibited. Involuntary movements were a frequent accompaniment of the attacks in the patients studied as well as in several patients the records of whose cases were collected from the literature, but these as well as similar movements observed during the attacks of somnolence are not entirely foreign to normal sleep. In addition to the thirty-one cases, four others are presented in which cataplexy or states similar to it occurred in the patients independently of attacks of sleep, the cataplexy being reactive in one patient and spontaneous in the other three. One patient in the latter group presented evidence of an injury sustained at birth; another apparently suffered from traumatic epilepsy, and a third had a tumor of the temporal lobe. Disturbances of nocturnal sleep, though not constant, were frequent in the main group of thirty-one cases. Six of the patients described "waking attacks" or states of delayed psychomotor awakening. Nocturnal restlessness so common in narcoleptic persons seemed to indicate a tendency for the normal cycle of sleep and waking to be replaced by a series of short attacks of rather superficial sleep.

With the exception of the patients who had had encephalitis, the results of neurologic examination were generally negative. Examination of the cerebrospinal fluid, however, revealed a slight to a moderate increase in the protein content or the number of cells in six of twelve patients with "genuine" cases as well as in all seven patients who had had encephalitis. Anomalies of the sella turcica, though varied, seemed sufficiently frequent to be of some significance. Encephalograms were made in eight cases; in four of these departures from the normal, all of questionable significance, were noted. Numerous signs of endocrine dysfunction were recorded, but there was no evidence of a causal relation between a disturbed function of any particular gland and the narcoleptic syndrome. Vagotonic phenomena were observed in every case. Relative lymphocytosis was a frequent, and prolongation of the sedimentation time of the red blood cells a constant, finding. The tendency to gain weight at about the time of onset or later showed a certain parallelism to the severity of the narcoleptic symptoms. The basal metabolic rate lay within the limits of normal in the majority of the patients; the rate was low in a few and high in a few others. The specific dynamic action of food, however, was diminished in eight of ten patients. Signs of a moderate impairment of the sexual function were relatively frequent. In no case could a narcoleptic attack be induced by hyperventilation.

Mental changes more or less characteristic of the postencephalitic state were noted in some of the patients with "genuine" cases as well as in five of the seven patients who had had encephalitis. The authors express the view that the lack of initiative and the slowing of the reactions frequently met with could hardly be accounted for by the drowsiness alone.

Improvement to a degree approaching complete recovery was observed in one of the three patients whose symptoms appeared subsequent to head injury; in another the symptoms disappeared following encephalography. Although partial remissions were not infrequent among the remaining patients of the entire group of thirty-one, marked and continued improvement was most unusual.

In discussing the pathogenesis and etiology of narcolepsy, Thiele and Bernhardt express the view, based on a consideration of the intimate relations existing between the principal symptoms, that it is essentially a disturbance of the sleep-regulating mechanism. The "cerebral obesity" and other vegetative disturbances frequently encountered in cases of narcolepsy furnish, in their opinion, some support for the general belief that the sleep-regulating center is located in the floor of the third

ventricle. A discussion of the hereditary factors, the frequency of onset in the second decade of life, the preponderance of members of the male sex among those afflicted and the influence of overexertion and shock leads to the conclusion that, in the "genuine" cases, a constitutional defect (*eine endogen bedingte Vulnerabilitat"*) plays the decisive rôle. Since the condition in the patients who had had encephalitis differed in no way from that in the others so far as the narcoleptic symptoms were concerned, Thiele and Bernhardt admit that some of the cases in which nothing suggestive of preceding encephalitis was found in the patients' history or on physical examination may nevertheless have been encephalitic in origin; further, that the recent pandemic of encephalitis may have had something to do with the increased frequency of narcolepsy. After discussing the posttraumatic cases and reviewing the pertinent literature, they take up the question of the relative importance of endogenous factors in relation to such exogenous factors as infection and trauma. In conclusion they express the view that in all cases of narcolepsy the "pathogenic mechanism" is essentially the same, regardless of the various etiologic agents which may serve to set it in motion.

The paper ends with a consideration of the matter of compensation for disability in cases of narcolepsy and of the various methods of treatment. Intrathecal injection of air for purposes of encephalography as well as of treatment was followed by apparent recovery in one of the patients studied; there was considerable improvement in another patient and temporary improvement in two others; in four patients the results were negative. Treatment with ephedrine exerted a favorable effect on the somnolence in four cases, although the results were indefinite so far as the cataplexy was concerned.

DANIELS, Denver.

ELECTRO-ENCEPHALOGRAMS IN MAN: IV AND V. H. BERGER, Arch. f. Psychiat. **97**:6 (June) 1932; **98**:231 (Nov.) 1932.

In these fourth and fifth reports on electro-encephalographic studies of the brain Berger presents oscillographic findings which corroborate previous results obtained with the use of the string galvanometer.

The original idea for the studies was based on experiments with the electrocardiograph, in which electric changes picked up from remote parts of the body afforded an insight into the function of the heart. The author undertook a similar study of the electric phenomena recorded by placing the electrode on the head. In these the electrocardiogram remained unchanged unless both electrodes were applied to the head. With the electrodes placed on the forehead and occipital region, however, one could exclude the cardiac waves. In order to avoid cutaneous surface phenomena, needle electrodes were used (silver electrodes plated with silver chloride), inserted deeply enough to touch the periosteum. The oscillograph permitted the recording of waves of a frequency of several thousand per second. The amplitude of the deflections allowed direct conclusions as to the voltage of the current picked up. Care was taken to avoid all disturbances. The subject was placed in a somewhat darkened room where all extraneous stimuli were absent. The recording apparatus was in an adjacent room.

Records obtained in this way showed two types of waves: (1) those of the first order, called *alpha* waves, of an average length, under normal circumstances, of from 90 to 100 sigma and an average amplitude of 0.2 millivolt, and (2) waves of a second order, called *beta* waves, of an average duration of from 20 to 50 sigma and with an average potential change of from 0.02 to 0.1 millivolt. The records were taken simultaneously with an electrocardiogram record to make sure that there was no interference. The wave frequency of the record is much lower than that of an electromyogram, so that no mistake in that direction is possible.

In order to ascertain the original source of the electric changes, Berger examined a number of patients following exploratory craniotomies. In these it was possible to insert the needle points into the dura mater. The record obtained was in every respect identical with the record from the surface of the skull. A record from the cortex itself obtained during the operation showed a similar picture.

Alterations in the normal electro-encephalogram were found in the following conditions: (1) During sleep there was a reduction of amplitude in the *alpha* waves. (2) In epileptic deterioration there were a marked increase in duration of the *alpha* waves and a decrease in frequency. (3) In children during the first weeks of life no *alpha* waves were recorded. In the third or fourth month they appeared with lower frequency and longer duration than in normal adults. In children aged 3 and 4 years a normal record was obtained. (4) In some feeble-minded persons normal records were found, whereas in other cases there was a reduction in the frequency of *alpha* waves. (5) In some mental diseases of organic nature (Korsakoff's psychosis, dementia paralytica and senile deterioration) a marked increase in the duration of the *alpha* waves was noted. (6) In chloroform anesthesia and under the effect of scopolamine the *alpha* waves disappeared completely. (7) Following epileptic attacks and during epileptic absences the *alpha* waves were completely absent for a time.

Of special interest are some alterations under normal conditions, which seem to be of theoretical importance. If a subject had been at rest at the beginning of the experiment and then was exposed to sensory stimuli which attracted his attention there was, after a latency period of about 0.3 second, a period of reduction and disappearance of *alpha* waves which was followed by a normal record. Furthermore, if a person was confronted with mental tasks, such as solving algebraic problems, a similar reduction of *alpha* waves was recognized while he was carrying on the work. Under none of these conditions were there any significant changes in the frequency and duration of *beta* waves.

Berger concludes that the *alpha* waves are manifestations of biologic activities in the central nervous system, closely related to the functions of the cortex, and that the *beta* waves are an expression of nutritive and metabolic processes in the tissues.

The disappearance of *alpha* waves in connection with reduction of cortical activity in stupor, in disease and in lower stages of development seems to fit in with this hypothesis. There appears to be a contradiction, however, between the findings during sensory stimulation presented in this study and the findings in animal experiments, in which increase in frequency and amplitude of action current waves was seen in the coordinated areas of the brain after sensory stimulation. The author believes that his records are not to be looked on as manifestations of activities in any special area of the brain, but of energy changes in the whole brain. He is of the opinion that his observations indicate that during special tasks or under the influence of special stimuli there is a redistribution of energy with increased activity in limited areas of the brain and a compensatory inhibition in the activities of the surrounding tissues. The argument that the absence of *alpha* waves might be due to continuous stationary excitation in the brain under the influence of stimulation is rejected on the basis of animal experiments, as well as on the fact that all electric phenomena accompanying nervous activities seem to be of aphasic type.

The author does not mention the interesting relationship which his findings bear to the work of Pavlov on stimulation and inhibition within the cortex. The work seems to have been carried out with great care. The low frequency of the potential changes which were recorded places them entirely apart from the records of muscle action currents. Further investigations will have to be carried out to ascertain whether these waves are actually products of activity of the brain.

MALAMUD, Iowa City.

THE NEUROGLIA (MACROGLIA) OF THE HUMAN BRAIN. S. RAMÓN Y CAJAL, Trav. du lab. recherches biol. de l'Univ. de Madrid **27:** (Appendix) 377, 1931-1932.

In 1913, Cajal created the gold sublimate method for staining glia cells and shortly afterward published an exhaustive study of the macroglia of the human brain. This paper, however, undoubtedly because it was published in Spanish,

remained almost unknown; therefore, Cajal's pupils have advised him to prepare a new French edition of his fundamental monograph. As a fact, this twenty year old paper is today on the whole as true as it was at the time of its first publication; later studies of macroglia have added little to Cajal's historic monograph.

The steps of the gold sublimate method are: 1. The brain tissue is fixed in liquor formaldehydi, 14 per cent (formaldehyde [40 per cent], 14 cc.; distilled water, 100 cc.) or, better, in formaldehyde solution (40 per cent), 14 cc.; ammonium bromide, 2 Gm., and distilled water, 100 cc., for one or two days or longer. 2. Frozen sections, from 30 to 35 microns thick, are placed directly in liquor formaldehydi, from 4 to 6 per cent, where they may be kept for several hours. 3. They are then washed in distilled water for a few seconds and transferred to the following solution: gold chloride (*brown* [Merck]) 1 per cent solution in distilled water, 10 cc.; corrosive sublimate, 5 per cent solution in distilled water, 10 cc.; distilled water, 50 cc. It is best to prepare the sublimate solution every time and while it is still hot to add the gold solution. The sections must lie flat at the bottom of the dish. Use 30 cc. of solution for every eight or ten sections. Avoid metal needles. The dish with the sections is kept in a thermostat in the dark until the sections acquire a violet color; several hours are necessary. The most favorable temperature for each part of the brain must be determined by trial. Generally a temperature of from 20 to 25 C. will give the best results. 4. The sections are washed in distilled water several times. 5. They are fixed in sodium hyposulphite, 6 Gm.; alum, 1 Gm.; distilled water, 100 cc., and concentrated solution of sodium bisulphite, 3 or 4 drops. 6. The sections are washed, dehydrated, etc. Special attention must be paid to the purity of the gold chloride and of the sublimate; the brain tissue must be fixed very soon after death, although in winter occasionally good results can be obtained even twelve or twenty-four hours after death.

Cajal describes the following types of glia cells: fibrous glia, protoplasmic glia and the third element, or cells without processes; there are transitions between the two first types.

In the protoplasmic glia cells Cajal described the nucleus; the protoplasm with its gliosomes, pigment, centrosome, reticular apparatus and other inclusions, and the processes of the cells, which divide repeatedly, generating a complicated ramification, and do not anastomose with those of contiguous cells, each cell thus being an independent unit. Besides the processes which end by means of free ramifications, the protoplasmic glia cells may have two other kinds of processes: one or several thick branches ending on the blood vessels, and processes enveloping the body or thick dendrites of contiguous nerve cells. The protoplasmic glia shows significant morphologic characteristics in different regions of the gray matter.

Cajal describes the main types of cells in different levels of the cerebral cortex. Of special interest is the fact that the small and medium-sized satellite cells do not have processes in contact with the blood vessels. These satellite cells were first described by Cajal in 1895. Among the satellites there are not only protoplasmic glia cells, but also cells of the "third element" class.

The fibrous glia is found chiefly in the white substance. Since it is more easily stained than the protoplasmic glia, it was better known when Cajal described his gold sublimate method; however, Cajal added interesting details on the fibrillar structures in the processes and in the perivascular endings.

The fractioning of glia cells in postmortem autolysis—clasmatodendrosis of Cajal—may appear as soon as two hours after death.

The last part of the paper deals with the "third element," of which the methods used by Cajal stained only the nucleus and protoplasm and not the processes. Cajal's description is complete so far as the distribution of these cells is concerned; he describes the following types: satellites of nerve cells, satellites of blood vessels, cells scattered in the gray matter and cells scattered in the white matter. This chapter of Cajal's monograph has no little historic interest, but, as Cajal points out in an additional note, the true significance of the third element

remained unknown until the publication of the studies of Rio-Hortega, who demonstrated that in it two types of glia cells were included, the microglia and the oligodendroglia.

In lower mammals (cat and rabbit), the neuroglia shows properties similar to those in man, except that the fibrous are more numerous than the protoplasmic type.

The gold sublimate method enabled Cajal to add interesting details to the description of the embryologic development of glia cells given many years before by His, Vignal, Golgi, Kölliker, Retzius and, chiefly, by himself. The new details refer mainly to the development of the perivascular endings and of the fibrils in the processes of the fibrous glia.

LORENTE DE NÓ, St. Louis.

FLUCTUATION OF AN AMBIGUOUS FIGURE IN DEMENTIA PRAECOX AND IN MANIC DEPRESSIVE PATIENTS. J. McV. HUNT and J. P. GUILFORD, J. Abnorm. & Social Psychol. **27**:443 (Jan.-March) 1933.

Starting with McDougall's theory that traits of personality are dependent on the rate of speed at which nervous impulses travel in the nervous system (thought to be relatively slow in the extrovert and speeded up in the introvert), the authors have sought to ascertain whether the same tendency can be shown to exist in the pathologic extremes of extroversion and introversion, namely, the manic-depressive and the schizophrenic psychoses, respectively. In order to carry his theory into the laboratory for substantiation, McDougall employed an objective test which consisted in noting the frequency with which his subject observed the change or flux in an ambiguous figure. The authors have previously reported a reproduction of McDougall's work on nonpsychotic persons (twenty-five male college students), employing as the test object a Wheatstone cube. They had found the average number of fluctuations of these normal men to be 18.06 fluctuations per minute when allowed to observe them passively and 9.50 fluctuations per minute when instructed to attempt to inhibit the shifts. Though the number of shifts per minute did not definitely indicate a trend of personality, such as could be correlated with introversion and extroversion scales, yet it was learned that wide differences in rates of fluctuation occurred for each subject and that these rates for that person were fairly constant from day to day, indicating that there was being measured some rather constant individual trait.

For the work on psychotic subjects, nineteen male patients from the Lincoln State Hospital with manic-depressive and twenty-six with dementia praecox psychosis were tested. Only subjects in whose cases the diagnoses were reasonably certain were used. The apparatus consisted of an electric counter, a telegraph key and the Wheatstone cube. The patients were instructed in both the passive and the inhibitive methods of observation. It was necessary to be en rapport with each patient before instruction was given. Thirty-nine patients were given the complete test of fifty-four minutes' duration divided into six three minute periods on three different days. Two subjects were never able to see a change, but their records were used because they were considered almost normal. Two subjects were first included and then discarded from the average because their rates were more than five times the probable error of the distribution above the average of their group. Early in the tests it was seen that the subjects with dementia praecox saw the first changes quickly and with little instruction. Patients with manic-depressive psychoses, on the other hand, were invariably slow in getting the first change. The reactions of the persons with paranoid dementia praecox were separated from the others because of a certain negativism which interfered with the smooth operation of the test.

The data compiled showed that the rate of fluctuation for the patients with dementia praecox is about four times that of the group with manic-depressive psychoses under passive instruction, 17.02 and 4.25 average shifts per minute, respectively, and about six times that of the group with manic-depressive psychoses under the inhibitive instructions, 13.10 and 2.24 average shifts per minute, respectively. The paranoid reactions subgrouped under dementia praecox had average rates of

12.20 and 5.17 changes per minute under the two types of instruction. There was more daily variation among the subjects with dementia praecox than among those with manic-depressive psychoses. The average rate for the group with dementia praecox, omitting those with paranoia, was found to be almost identical with that of the normal group.

The authors conclude that the difference in the rate of fluctuation found for pathologic subjects manifests itself entirely as an inhibition of the fluctuation in cases of manic-depressive psychoses. In other words, patients with manic-depressive psychoses are the real deviates from the normal range in the rate of fluctuation perceived.

WISE, Howard, R. I.

CHOKING OF THE OPTIC DISKS IN DISEASES OTHER THAN TUMOR OF THE BRAIN. JOHN T. STOUGH, Arch. Ophth. **8**:821 (Dec.) 1932.

In making a diagnosis of intracranial tumor, the physician seeks for the presence of what is known as choking of the optic disk. Evidence favors the view that it is due to an obstruction of the internal flow of blood from the retina, with perhaps also obstruction of the lymphatic drainage of the retina. If the ophthalmologist could always be certain of the diagnosis of choking of the optic disks, and if this finding were produced only by intracranial tumor, it would be helpful. Unfortunately, choking of the optic disks may be simulated by other conditions of the retina, and actually produced by diseases other than intracranial tumor. The author, as with all ophthalmologists, reports cases of definite choking of the optic disks with other symptoms suggestive of intracranial tumor in which the subsequent course of the disease seemed definitely to rule out this diagnosis. These included cases of optic neuritis, cases due to infection about the teeth or the sinuses, the retinitis of cardiovascular renal disease and cases of hypertension without marked renal or cardiac lesions, in which the fundi presented a picture identical with that of choking of the optic disks with increased intracranial tension.

In some of the cases, especially those accompanied by cerebral arteriosclerosis with bilateral choking of the optic disks, the symptoms of the head were so definite that ventriculograms and special pictures were taken. Naturally, all of them showed normal conditions.

In one case of acute lead poisoning, the neurologist stated that he was of the opinion that an intracranial tumor was present. In three other cases, no definite diagnosis was ever made as to what the cause of the choking was. In one case, that of a child, aged 4 years, a neurologic examination revealed a cracked-pot resonance of the head, hypotonia of the extremities, decomposition of the movements of the left hand and, at times, a bilateral Babinski phenomenon. This patient also showed a bilateral paralysis of the sixth nerve. The patient had from 3 to 4 diopters of swelling with numerous hemorrhages. Roentgen examination revealed a diastasis of the sutures and digital markings on the inner tables of the skull, pointing to an increase of the intracranial tension without localizing signs of a tumor of the brain. A midline cerebellar tumor was suspected. A suboccipital decompression and cerebellar exploration, however, revealed nothing abnormal. Following this operation, roentgen treatments were given. The patient completely recovered.

Another child, also aged 4 years, with very similar neurologic findings, had a similar exploratory operation. In this case a greatly dilated posterior cistern was discovered, but no tumor. After a rather stormy convalescence, this child also made an uneventful recovery. (It seems to the reviewer that this case could well have been an inflammatory, posterior arachnoiditis.)

The last case mentioned in the series was one in which a diagnosis of bilateral papilledema had been made after an illness of two weeks. Here, also, there were neurologic symptoms; dizziness without loss of consciousness, weakness of both legs and tingling of the right leg. Roentgenograms of the head gave absolutely

negative findings. No operation was performed in this case. The child's fundi, after a period of six months, showed a rather high degree of atrophy of the bilateral optic nerve, probably of a secondary nature. The author, in his concluding comment, calls attention to the fact that the condition in this case as well was probably inflammatory and could have been one of encephalitis.

SPAETH, Philadelphia.

OBSERVATIONS ON THE AETIOLOGY AND SYMPTOMATOLOGY OF DISSEMINATED SCLEROSIS. W. J. ADIE, Brit. M. J. **2**:997 (Dec. 3) 1932.

Adie studied 70 cases of acute retrobulbar neuritis and 118 of established disseminated sclerosis. The latter is the most common condition encountered in private neurologic practice. Genuine familial cases do occur. In this series 58 per cent of the patients were females. Nothing is known of the cause of the disease. The nature and mode of onset are extremely variable. The following initial symptoms and their rate of incidence in the patients whose cases were studied are recorded: transitory ocular disturbances (amblyopia, diplopia, etc.), 40 per cent; transitory or variable motor or sensory disturbances in one or both lower limbs, 30 per cent; the same in one or both upper limbs, 6 per cent; the same in the homolateral arm or leg, 5 per cent; severe attacks of vertigo, 4 per cent, and numbness of one side of the face, 3 per cent. The course was discontinuous in every case. The age at onset was in the third or fourth decade in 74.5 per cent of the patients. The earliest age at onset was 12 years. Cases beginning after the age of 45 are doubtful. Very long remissions occur, especially when acute retrobulbar neuritis is the first symptom. The longest remission noted in this series was thirty-two years.

Some uncommon symptoms were attacks of jacksonian epilepsy, with spasms in one arm and with gross loss of postural sense during the intervals; acute attacks of vertigo; repeated vomiting; unilateral attacks of pain or of numbness; a feeling of electric shocks in the body, and in one patient, pain in the area of distribution of the first lumbar roots on coughing. The incidence of nystagmus is high, but this condition is frequently absent. Paresis of an ocular muscle producing diplopia is common, but a gross detectable squint is rare. Lasting gross ocular palsy is rare. Transient diplopia may precede all other signs and symptoms by years. Alterations in the pupils, except those associated with acute retrobulbar neuritis, are very rare. Lesions in the optic nerves, chiasm and tracts are common; permanent blindness or even permanent severe loss of vision is rare. Mild transitory attacks of amblyopia are common.

Of the 118 patients analyzed, a clear history of a severe attack of acute retrobulbar neuritis was obtained in 41. In many it was the first symptom, and in every instance it was an early symptom. Simultaneous involvement of both eyes was not once recorded. Early consecutive attacks are very rare.

Acute retrobulbar neuritis is characterized by an acute onset, unilateral incidence, "central" scotoma and a tendency to recovery. Pain is usually present at the onset, at rest, on involuntary movement, or on pressure on the eyeball. Failure of vision is rapid and usually reaches its maximum in from a few hours to a day or two. The visual defect is most intense in the central area of the field and may be reduced to perception of movements of the hand or less. Recovery usually begins within a week or two and may be almost complete by the end of from six weeks to two months. In the acute stage visible changes in the disk are rare. Mild swelling is later apparent.

In the opinion of Adie, disseminated sclerosis is the only known common cause of acute unilateral retrobulbar neuritis. There are other rare allied acute inflammatory diseases of the nervous system. Of 70 patients with acute retrobulbar neuritis who were examined within a week or two of the onset, 31.3 per cent were already suffering from disseminated sclerosis, while in 41.8 per cent the diagnosis was "probably disseminated sclerosis."

FERGUSON, Niagara Falls.

CHRONIC SUBDURAL HEMATOMA: A LATE COMPLICATION OF CRANIAL TRAUMATISM. P. VAN GEHUCHTEN, Rev. d'oto-neuro-opht. **10**:651 (Nov.) 1932.

Subdural hematomas are supposed to be the result of two causes: Some are spontaneous and develop progressively, while others are the consequence of cranial traumatism. The symptoms begin several days or even months after the initial trauma with headaches and important changes in character, and end in the picture of intracranial hypertension. Crises of headache, vertigo and vomiting characterize this stage. Papillary stasis occurs in half of the cases. Focal symptoms are variable in intensity. The spinal fluid is generally under increased tension, and most often there are albuminosis and a slight lymphocytosis. In recent cases the spinal fluid is hemorrhagic or xanthochromic. A fatal case with autopsy observations is reported. Excellent reproductions of photomicrographs are included.

The patient suffered a violent fall on the head with loss of consciousness. He was able to return to work after a few days. Two weeks later, progressive disturbances of gait, headaches, changes in character and loss of memory occurred. Death in coma supervened five weeks after the accident. At autopsy, a subdural hemorrhage covering the greater part of the right hemisphere was observed. The hemorrhage was separated from the pia by a membrane. In the anterior part of the area was a small encysted hematoma, 4 by 2 by 1 cm. The cyst contained a brownish-yellow clot. All around the cyst the dura was covered with a thick membrane that was adherent to it. This membrane, which replaced the arachnoid, extended to almost the whole convexity of the brain. The cyst and the area of hemorrhagic pachymeningitis were examined microscopically. Immediately under the dura, and in close connection with it, the external membrane of the cyst was formed of loose connective tissue with elongated nuclei, in the meshes of which lay large vascular spaces lined with endothelium and numerous cells filled with pigment. The cyst was composed of a mass of well preserved red blood cells and was crossed by strands of connective tissue. The internal membrane was delicate, was made up of fibrils of connective tissue with small nuclei and contained cells filled with pigment. The innermost layer was formed by the arachnoid. The zone of hemorrhagic pachymeningitis was continuous with the cyst. The dura was almost normal. Closely adherent to it on the under side was a thick membrane, the external part of which was composed of loose connective tissue containing large vascular spaces; the inner part was formed by dense connective tissue. The membrane was highly vascularized and in places contained true hemorrhagic foci. Inside it was the arachnoid, which was closely adherent to it in many places. The meshes of the connective tissue contained numerous microphages loaded with pigment.

Van Gehuchten concludes from a study of a case of spontaneous hematoma that there is no essential difference between it and posttraumatic hematoma. Both develop progressively from repeated hemorrhages. The aspect of the cyst and its membranes is the same in both cases. The etiology is discussed without a definite conclusion being reached. The question as to whether the condition is due primarily to a pachymeningitis, which ultimately is the cause of the successive hemorrhages, or whether there is a sort of hemorrhagic diathesis of the meninges, which later causes the pachymeningitis, cannot be decided from the available data.

DENNIS, Colorado, Springs, Colo.

SIMMONDS' DISEASE. SOLOMON SILVER, Arch. Int. Med. **51**:175 (Feb.) 1933.

American literature on Simmonds' disease is scanty; Silver was able to find only one case previously reported in the English language. To this he adds a second case, that of a woman, aged 53, who, having been married at the age of 20, had had eight pregnancies. At 40, shortly after the birth of her last child, the menses ceased, and the patient began to experience fatigue. She weighed 130 pounds (59 Kg.) at that time but began to lose weight, and within twelve years was down to 60 pounds (27.2 Kg.). Her teeth had become carious and had fallen

out. Menses and libido had been absent since the age of 40. An examination showed extreme cachexia with atrophy of the breasts and of the external genitalia, and sparseness of pubic and axillary hair. Neurologic examination gave negative results. The blood pressure was 120 systolic and 80 diastolic. The hemoglobin was 47 per cent, and the basal metabolic rate, —10 per cent. A roentgenogram of the sella turcica showed no abnormalities. The woman died. Autopsy showed the absence of panniculus adiposus and an atrophy of the heart, liver, kidneys and all other organs. The pituitary body was smaller than normal, and disclosed extensive fibrosis and reduction in the parenchymatous elements of the anterior lobe. There was marked degeneration of the cells of this lobe.

Reviewing the literature (presenting a bibliography of ninety-five references), Silver is able to construct the clinical picture. The disease occurs commonly in middle life and is excessively frequent in women as compared with men. The onset is insidious and often follows a complicated labor. It seems to occur more commonly in women who have had repeated pregnancies. The outstanding symptom is cachexia, which is more extreme than that found in tuberculosis or even in carcinoma. The patients look senile; the skin is wrinkled, loss of teeth and atrophy of the mandible are noted. The external and internal genitalia atrophy in both sexes. Hair, including moustache, beard and axillary hair, becomes sparse and tends to fall out completely. Mental disturbances are often conspicuous. Although headache is a common complaint, it is not characteristically of the pituitary type. The blood pressure, the pulse rate and the hemoglobin count are invariably low. The metabolic rate is always depressed—a finding which distinguishes Simmonds' disease from the cachexia of tuberculosis or of malignant disease in which a high basal metabolic rate is the rule. This finding plus the atrophy of the external genitalia and the corresponding loss of libido, combined with the extreme cachexia, serves to establish the diagnosis.

The site of the disease is the anterior lobe of the hypophysis. The lesion is destructive in nature, and almost every pathologic agency has been reported. Infection, embolism, injury, tumor, tuberculosis and abscess have been found in various cases as underlying causes of atrophy of the anterior lobe. Because the disease is the physiologic converse of acromegaly, Silver suggests that it depends on hypofunction of the eosinophilic elements of the pituitary gland, just as acromegaly is associated with hyperfunction of the same cells. Logically, replacement therapy seems indicated, and good results from the use of the anterior lobe of the pituitary gland have been claimed. Insulin, from 2 to 20 units before meals, may be useful in increasing appetite and weight. The disease is probably more common than is generally supposed.

DAVIDSON, Newark, N. J.

HEADACHE PRODUCED BY HISTAMINE AND ITS MECHANISM. GEORGE W. PICKERING and WERNER HESS, Brit. M. J. **2**:1097 (Dec. 17) 1932.

The purpose of this study was to determine, if possible, the cause of histamine headache. When histamine is injected intravenously in normal subjects, the following phenomena appear: After about twenty seconds a metallic taste is felt in the mouth, and simultaneously the face flushes and systolic and diastolic blood pressures begin to fall. If lumbar puncture is performed, the cerebrospinal fluid pressure is found at this time to rise suddenly. Changes in facial color, in arterial blood pressure and in cerebrospinal fluid pressure progress for a further period of from ten to twenty seconds, and then begin to pass away. Headache begins about forty seconds after the onset of vasodilation, when the facial flush is just beginning to fade, when arterial pressure is at its resting level or above, and when lumbar pressure is falling from its peak value. The headache reaches a maximum about half a minute after its onset, begins to lessen about a minute later, and finally disappears after it has been present for from six to ten minutes. The headache is at first conspicuously throbbing, waxing and waning with the pulse beat, and tending to become continuous, uninfluenced by the pulse during the last three or four minutes of its duration. It usually begins in the forehead and continues most

intense in this location; it tends, at its height, to invade the temples, the convexity of the calvarium and occasionally the occipital region. Thus, following injection of histamine, two phases are recognized: one, of vasodilation and the other, the disappearance of this phenomenon.

That the headache arises in the meninges is suggested by the observation that it is always greatly increased by a rapid oscillatory movement of the head about either a horizontal or a vertical axis, this causing a straining of the meninges. Raising intracranial pressure relieves the headache. A similar effect is produced by artificially lowering the blood pressure. This suggests that the headache arises from stretching of the walls of the cerebral arteries or the tissue in their immediate vicinity, for the headache is inhibited either by a rise of pressure outside these vessels or by a fall of pressure within them. It is somewhat difficult to explain why the headaches outlast the objective signs of the vasodilation. The author suggests that two hypotheses are possible. First, the dilator action of histamine on the cerebral arteries may conceivably outlast its action on the minute vessels. If this were so, then the loss of tone of the cerebral arteries might not at first result in their expansion, since this would be prevented by the rise of pressure outside these vessels and the fall of pressure within them; the expansion of the arteries would occur as intracranial and arterial pressures returned to their normal levels. Thus, overexpansion of the cerebral arteries would be the cause of histamine headaches. The second hypothesis is that cerebral vasodilation may redistribute cerebrospinal fluid in a manner that is not immediately reversible when vasodilation subsides. The authors emphasize that they do not claim or believe that all headaches arise in this way, but that in headaches due to histamine there is evidence that they are to be ascribed to a state of tension set up in the meninges.

FERGUSON, Niagara Falls.

TUMOR OF THE TECTUM MESENCEPHALI WITH THE CLINICAL PICTURE OF ENCEPHALITIS LETHARGICA. B. BORNSTEIN, Jahrb. f. Psychiat. u. Neurol. **49**: 46, 1933.

A man, aged 35, two weeks before admission to the hospital, had fatigue and a dull nonlocalizable headache. These symptoms persisted till the day of admission, when there also appeared fever and somnolence. He slept almost continuously, but could be aroused readily. When awake he was fully conscious and answered all questions correctly. The patient was neither syphilitic nor alcoholic. Examination revealed a well developed and well nourished man with deeply injected mucous membranes. He was lethargic, but when aroused said that he was sleepy. There was slight rigidity of the neck, but no Kernig sign. There was no tenderness on percussion of the skull. The pupils were round, but did not react to light and only slightly in accommodation; there was no nystagmus. There were some limitation of lateral gaze, ptosis of the right upper lid and a shallow nasolabial dip on the same side. Speech was a bit nasal and slurring. There were no other neurologic signs. Toward evening of the day of admission, the general condition became worse, the speech more slurred and he complained of diplopia. At this time the right pupil was larger than the left, and the right internal rectus muscle became paralyzed. The patient slept well during the night; the next morning the temperature was 37.9 C. (100.2 F.), and he perspired excessively. The meningeal signs increased; the left pupil became more dilated, and the pupils reacted neither to light nor in accommodation. Breathing became more rapid and the somnolence more profound and continuous, although he could still be aroused. The fundi showed no abnormalities. Lumbar puncture was not performed. Examination of the blood and urine showed no deviations from the normal. Death occurred forty-eight hours after admission. The clinical diagnosis was encephalitis lethargica ophthalmoplegica.

Necropsy revealed a richly cellular, infiltrating tumor in the region of the roof of the inferior corpora quadrigemina. Almost the entire roof was displaced by the lesion, which extended to the aqueduct so that the latter was distorted and

reduced to a narrow slit, and a small cork-shaped piece of tumor tissue projected through the roof into the lumen of the aqueduct. The normal structure of the tectum was lost. Ventrally, the tumor reached the tectal fiber system without actually involving it. The trochlearis on one side (the side is not mentioned) was caught in the tumor. No tumor tissue was found in the region of the oculomotorius nucleus, although this structure appeared swollen and edematous. The oral portion of the medulla, i.e., at the transition between the fourth ventricle and the aqueduct, as well as the pons, showed no evidence of invasion. The tumor was a rapidly growing glioma.

KESCHNER, New York.

THE BIOLOGICAL AND SOCIAL BACKGROUND OF A TANTRUM CASE. E. C. ROWE, Ment. Hyg. **16**:610 (Oct.) 1932.

Rowe believes that in explaining temper tantrums as a form of response, there is a tendency to place too much emphasis on training and too little on hereditary qualities. It is his contention that there are great individual differences in the ease with which this pattern of response is acquired, and that these differences depend on inherited characteristics. The hypothesis is illustrated by the report of the case of a girl, aged 12, who lived with her mother in an orphanage. The girl was physically well developed and free from illness, and had an intelligence quotient of 123. Eager and active, she was readily moved to tears or to outbursts of extreme anger. This cannot be accounted for on the assumption that the mother "spoiled" the child by catering to her whims, for the fact is that the tantrums appeared at the age of 2, and that the mother ignored or punished them for several years, adopting the policy of indulgence only after sterner methods had failed. An equally intelligent, but emotionally much more stable, older brother, who had been subjected to an early training in every way similar to that of the girl is cited as an evidence of the relative ineffectiveness of training as an explanation of the tantrums. An investigation of the family history showed different emotional trends in the two sides of the family. The father was good-natured and easy-going; the mother as a girl had been a sulky, pouting child, and was herself the daughter of a stern, "hot-tempered" father. It is Rowe's opinion that the boy can be described as a replica of his father, while the girl possesses the temper of her mother and maternal grandfather. The existence of significant environmental factors, however, is not denied. At the age of 6 the girl was placed in a dormitory with thirty other children; the matron was a stern disciplinarian. The other children, intellectually inferior to the patient, lost no opportunity of taunting her, to compensate for their own feeling of inadequacy. The girl's mother had been promoted, and the older members of the orphanage force resented this advancement and treated the child accordingly. The mother was eventually placed in a position in which she was obliged to report girls for misbehavior, a situation that further stimulated mistreatment of the patient. As no mention is made of the disposition of the brother, the presumption is that he was living in a more sympathetic environment.

The author concludes by discussing the technic of the individual management of problem children of this sort. That improper training can produce the temper tantrum pattern of response is not denied, but a plea for the recognition of the hereditary factor is made.

DAVIDSON, Newark, N. J.

OCULAR MANIFESTATIONS OF LESIONS OF THE FIFTH CRANIAL NERVE. R. FOSTER MOORE, Brit. M. J. **2**:783 (Oct. 29) 1932.

Involvement of the gasserian ganglion may occur in the spread of inflammation from the middle ear, producing unilateral headache; in basic meningitis; in a tumor of the cerebellopontile angle, or in inflammation or neoplasm in any part of its peripheral course. The ganglion is the trophic center for all the sensory branches of the fifth nerve. In the involvement of an organ which it supplies, referred pain may be important. Thus, pain resulting from an inflamed iris, if it is prolonged and severe, may cause a spread from the afferent impulses to adjacent cells in the

ganglion, so that pain is referred to the side of the nose, the orbital margin, the side of the face, or the meninges, causing headache, or may even spread to the vagus center and cause vomiting. The opposite nucleus may be similarly involved from severe or prolonged afferent impulses.

"Herpes zoster appears to be an acute specific disease, some product of which shows a selective activity for the ganglion cells." Posterior poliomyelitis has been suggested as an appropriate name for it because it so closely parallels anterior poliomyelitis. It is more common in middle age, but has been reported in young children. The first manifestation is pain of a burning or lancinating character in an area which three or four days later will be the seat of the rash. Hyperalgesia, erythremia, vesiculation, rupture of the vesicles, cicatrization and anesthesia appear. Because of a meningeal branch from the ophthalmic nerve, headaches and vomiting may occur. Lacrimation is not affected. Involvement of the mucosa and outer wall of the nose may be an unpleasant complication. The most important complications result from involvement of the eye and include corneal diseases, iridocyclitis, ocular palsies and optic atrophy.

"The pathology of herpes zoster raises the question of the occurrence of antidromic impulses." The sequence of infection of the ganglion cells, pain and then a rash, suggests this possibility. Other explanations might be the breakdown of nerve fibers in the skin or the transmission of the products of cellular breakdown in the ganglion to the skin, as seems to occur in the case of the toxins of tetanus.

Moore also discusses the corneal nerve fibers which can be seen by means of the slit lamp. The explanation of neuroparalytic keratitis is not definite, but the chief controversy ranges about the question of the existence of trophic nerves. Anesthesia of the cornea alone will not produce ulceration, for if the cornea is completely protected, as by tarsorrhaphy, it does not develop. The fact that ulcers occur perhaps years after "mustard gas" poisoning suggests to Moore a neuropathic element.

FERGUSON, Niagara Falls.

MENTAL HYGIENE AND THE DEPRESSION. DOUGLAS A. THOM, Ment. Hyg. **16**:564 (Oct.) 1932.

Experiences in the war and in the present economic depression emphasize two important facts: 1. There are at any given moment a vast number of persons who are carrying on with apparent success but who are just on the verge of an incapacitating mental illness. 2. For every person there is probably a limit to the strain, mental or physical, that he is capable of withstanding without reaching the breaking point. There is a strong feeling among psychiatrists and sociologists that the mental stresses of the past two years will give evidence to support the contention that there is a definite relationship between a general attitude of pessimism bred by the depression and various sociologic problems.

The number of first admissions to the State Hospitals per hundred thousand population in New York was 77 in the prosperous year 1928, and 76.9 in the year 1931; in Massachusetts the corresponding figures were 75 and 70.8. This suggests as yet no increase in the incidence of insanity as a result of the depression. Institutions for mental defectives show a different picture. The number admitted in Massachusetts in 1929 was 304; in 1931, 461. It appears that in times of depression there is a tendency to seek custodial care for mentally defective children. The figures of the Veterans' Bureau contrast markedly with those of state hospitals. The latter showed a decrease in admission rate since the beginning of the depression; the patients from the Veterans' Bureau admitted to the neuropsychiatric division of the federal hospitals, on the other hand, doubled in the last three years. In 1928, there were 2,900 first admissions in this class; in 1931, there were more than 5,000. This does not indicate any increase in mental disease; it merely shows that a large group have found the generosity of the government a staff on which to lean in time of trouble. While there is, therefore, no evidence of any serious and immediate direct effect on the mental health of the country, there can be no doubt that there will be eventual devastating and intangible sequelae. Certainly

millions of people have had their attitude toward life twisted and distorted by an ever-present sense of economic insecurity. Harassed parents, panicky at the thought of starvation and neglect for their children, have become impatient and critical, selfish and suspicious, while children have had to choose between the unwholesomeness of the unguarded street and the unwholesomeness of the turbulent home.

Today is the time to apply mental hygiene principles in a practical way. The psychiatrist must not emulate the one-sidedness of his organically minded brother who was blind to the mental aspects of the patient's life, by being blind himself to the economic and sociologic phases of the problems of his patients.

DAVIDSON, Newark, N. J.

FURTHER REPORT ON THE TUBERCULIN TREATMENT OF ASTHMA. JAMES MAXWELL, Brit. M. J. **2**:1182 (Dec. 31) 1932.

The series of thirty-six cases of patients with asthma treated by tuberculin, described in 1930, has been followed up, and the present state of the cases is recorded. There has been a tendency to relapse, so that the present results are less encouraging than those previously recorded. The cases of patients treated subsequently, up to and including 1931, are added, bringing the total treated to 103.

With regard to the indications for the use of tuberculin in asthma, it is impossible to lay down hard and fast rules. In the first place, physical abnormalities in the upper respiratory tract should be corrected when possible; gastro-intestinal dysfunction should be relieved, and an attempt should be made to assess the psychologic state of the patient before tuberculin treatment is considered. Then, too, allergic sensitization tests should be carried out. If there is a well marked sensitiveness to a single avoidable protein, tuberculin treatment may not be necessary. In all other cases, if the asthmatic state remains, a course of tuberculin should be attempted.

In this series there were six patients in whom a marked neurotic element was present. The results of treatment in all showed complete failure. In cases in which there is an infection of long standing in the respiratory tract, it may be preferable to adopt treatment by means of an autogenous vaccine. At times tuberculin may succeed when a vaccine has failed, and vice versa, but the results generally are not satisfactory. Tuberculin does not appear to have any effect on other allergic conditions so frequently associated with asthma. In no case of hay fever was any benefit noticed. Failure of treatment is easily recognized and may be admitted if there is no improvement after two months. Increase in frequency and severity of attacks at any stage in the treatment may indicate merely that the dose is too high. The commonest apparent causes of failure in the present series have been overdosage, premature termination of the course and marked psychologic abnormality in the patient.

Maxwell concludes, on the basis of this study, that the tuberculin treatment of asthma yields results which, although less promising than they appeared to be at first, are still sufficiently good to warrant a trial of tuberculin in all apparently suitable cases.

FERGUSON, Niagara Falls.

THE CEREBROSPINAL FLUID PRESSURE AND THE EFFECTS PRODUCED BY EXPERIMENTAL CHANGES IN ITS QUANTITY. K. HAUG, Arch. f. Psychiat. **97**:303 (July) 1932.

Using the method that was applied in the study of changes in the cerebrospinal fluid pressure as determined by serial manometric readings (Klinische und pharmakodynamische Untersuchungen des Liquordrucks vermittelst Dauerdruckmessungen bei Geisteskranken, *Arch. f. Psychiat.* **97**:185, 1932), Haug studied: (1) the return to normal pressure after removal of certain quantities of spinal fluid in eight persons; (2) the return to normal pressure following the injection of physiologic solution of sodium chloride in six persons and of cerebrospinal fluid in four persons, and (3) the effect on the pressure produced by pharmaceutic reagents after the

removal of spinal fluid (0.01 cc. of pilocarpine hydrochlorate injected subcutaneously in five patients, 0.001 cc. of atropine sulphate injected subcutaneously in four patients, 20 cc. of distilled water injected intravenously in two patients, 20 cc. of a 20 per cent physiologic solution of sodium chloride injected intravenously in two patients and 40 cc. of a 50 per cent solution of dextrose injected intravenously in two patients).

After the removal of from 5 to 20 cc. of cerebrospinal fluid the pressure returned to normal in from forty to ninety-five minutes. The time necessary for the return to normal pressure was proportionate to the amount of fluid removed. After the injection of 10 cc. of physiologic solution of sodium chloride the pressure fell to normal after about thirty minutes. After the injection of cerebrospinal fluid the return to normal occurred in about forty-five minutes. The injection of atropine retarded the rate of return, whereas the injection of pilocarpine caused acceleration. Hypertonic and hypotonic solutions injected intravenously did not show any consistent effects on this process.

Haug believes that the return to normal pressure after the removal of some cerebrospinal fluid depends mainly on the regeneration of the fluid, and that this can be influenced by drugs. The incidence of headache and other complaints following spinal puncture seems to depend on the amount of fluid removed and therefore is apparently related to the regeneration of the fluid.

MALAMUD, Iowa City.

PHYSIOLOGY OF OLFACTION. HEYNINX, Rev. d'oto-neuro-opht. **11**:10 (Jan.) 1933.

Zwaardemaker's classification of odors on the basis of chemically pure odorant bodies *(odorivecteurs)* is the most logical one: ethereal, aromatic, balsamic, ambrosial, alliaceous, empyreumatic, capryllic, repulsive and nauseous odors, the odorivector type being represented, respectively, by iso-amylacetic ether, nitrobenzene, terpineol, musk, ethyl bisulphide, guaiacol, valerianic acid, pyridine and scatol.

After depicting the anatomic configuration, location and minute structure of the olfactory area, Heyninx discusses the mode of action of odorific bodies on the olfactory end-organ and apparently substantiates the assumption that the action is physical. The vapors given off by the odorant bodies are carried in the inhaled and exhaled air through the nose and are condensed on the olfactory area where, by their molecular vibration, they disturb the hairs of the olfactosensorial cells of Schultze. In 1872, Sellmeyer demonstrated that the wavelength of the molecular vibrations of bodies is found by determining the wavelength of their spectral bands of absorption. Heyninx, after determining that the diameter of the grains of olfactory pigment in the epithelial cells of the olfactory area amounts to 0.3 micron or less (which places their vibratory frequencies in the ultraviolet range), studied the ultraviolet bands of absorption of about forty odors, with the following results: 1. The bands of absorption of inodorous bodies were below a wavelength of 0.2 micron, while the bands of absorption of the odorous bodies were between the wavelengths 0.2 and 0.36 micron. The ultraviolet bands of absorption embrace from 0.1 to 0.4 micron wavelengths. 2. Odors were classified according to their wavelengths and arranged in a progressive scale, forming an olfactory keyboard. This classification is then simplified by including only the seven fundamental odors: ethereal, vanillic, spiced, burnt, fetid, rotten and acrid. This classification will serve as a basis for the construction of an olfactometer by which may be traced the curves of sensory acuity of the whole olfactory keyboard; Heyninx is now perfecting such an instrument.

This lucid and concise article is accompanied by explanatory charts and diagrams, and will amply repay reading in full.

DENNIS, Colorado Springs, Colo.

THE HINDBRAIN OF THE OPOSSUM, DIDELPHIS VIRGINIANA. H. C. VORIS and N. L. HOERR, J. Comp. Neurol. **54**:277 (April) 1932.

This study deals with the external anatomy of the hindbrain of the opossum and its most important cell groups. The distinguishing features of the medulla are the dorsoventral flattening, the large size of the trigeminus, corpus pontobulbare, trapezoid body and restiform body, and the small size of the pons and pyramids. There are no striae medullares acusticae. The fissural pattern of the cerebellum is comparatively primitive.

Microscopic analysis includes description of twenty-one typical cross-sections between the level of the posterior part of the inferior colliculus and that of the first cervical segment, and construction of projections of all the primary sensory and motor nuclei of cranial nerves and of many of the coordination and reflex centers of the medulla. These projections were based on two transverse series, a Weigert and a silver preparation. Histologic descriptions are based, in addition, on transverse Nissl series of adult and pouch-embryo preparations, and other sagittal and horizontal series of Weigert and silver preparations.

The tractus solitarius in this animal has two nuclei, a medial and a lateral. The lateral nucleus is much the smaller and is seen in the rostral part of the tract only so far caudally as the middle of the vagal portion. The corpus trapezoideum is almost superficial on the ventral surface of the brain. The nuclei of the cerebellum are in three groups—a lateral nucleus, a medial nucleus fastigii and an intermediate nucleus. The nucleus of the restiform body appears to receive fibers from the contralateral inferior olive and from the homolateral nucleus cuneatus.

The descriptions include also coordination and reflex centers of the medulla, the cerebellar peduncles, nuclei of the lateral lemniscus, nuclei of the superior and the inferior olives, the nucleus of the brachium conjunctivum, pontile nuclei, nuclei of the lateral funiculi, external arcuate nucleus and nuclei of the clava and tuberculum cuneatum.

This comprehensive study of the anatomy of the brain of the opossum is to be followed by a functional analysis of the cranial nerve nuclei and the conduction systems of the hindbrain.

ADDISON, Philadelphia.

PRACTICAL UTILIZATION OF DREAM ANALYSIS. W. M. KRANEFELDT, Arch. f. Psychiat. **96**:219 (March) 1932.

This paper, which was read by the author at the General Medical Congress for Psychotherapy, May 14, 1931, deals with a presentation of C. G. Jung's theory of dream analysis. He introduces the subject by statements concerning the importance and value of dream analysis in the treatment of mental diseases. The most important dreams are those which are brought by the patient at the beginning of the treatment, and which he calls the initial dreams. They usually represent the inner life of the patient and the fundamental difficulties which have led to the development of the symptoms. He does not think that very deep analysis and intricate interpretations are necessary to see through the meaning of the dream. This meaning, however, may be somewhat disguised, and it is essential that the physician gain an appreciation of the relationship between the dream and the life experiences of the patient. It is furthermore equally important to have the patient understand this relationship. Where either or both fail to gain such an understanding, the dreams become more and more complicated and obscure. The dreams have the further value of expressing frequently the relationship of the patient to the physician, and serve as indicators of certain steps that the physician should take, including the one of the possible breaking of the analysis. It is also important, according to the author, to have the patient take an active interest in the interpretation of his dreams, and for that purpose it may be advisable to have the patient keep a record of his dreams and attempt to see the relationships of the different dreams to one another and of all of them to his own problems. A discussion of the relative merits of this type of appreciation and that of the freudian school is interspersed throughout the paper, but unfortunately frequently remains on a rather superficial level.

MALAMUD, Iowa City.

NEUROPARALYTIC ACCIDENTS COMPLICATING ANTIRABIC TREATMENT. G. STUART and K. S. KRIKORIAN, Brit. M. J. **1**:501 (March 25) 1933.

Three instances of paralysis are recorded following treatment with a killed phenolized rabies virus vaccine. Two of the cases ended fatally as Landry's paralysis. In the other, there was paresis of the lower extremities. In the last case recovery took place without loss of control at any time over the urinary and rectal sphincters. Such paralyses are rare in either the young or the old. The one fatal case was in a person 29 years of age; the other patient was 5 years old. The third case was in a girl aged 5. No previous cases have been reported among members of the age group 5 or under. Statistics have proved the superiority of phenolized vaccine over all others, but these three cases prove that the safeguards are far from being absolute.

Necropsy in the two fatal cases showed almost a complete absence of gross pathologic alterations. In the second case the vessels were somewhat congested, and small hemorrhages were noted throughout the nervous system. The histopathology differs from that previously published. There was very little more than varying degrees of degenerative change in the nerve cells, together with considerable vascular congestion and occasional hemorrhage. Evidence of perivascular demyelinization and of perivascular cuffing was altogether wanting. The absence of Negri bodies and of perivascular and periganglionic infiltrations differentiates the condition from rabies.

A cytotoxin, rather than a virus theory of origin, is again advanced. Thus, in the basic nerve substance of all antirabic vaccines there seems to exist some deleterious component which, though adversely affected by various physical and chemical agencies, is still capable, in peculiarly susceptible persons, of producing neuroparalytic disorders.

FERGUSON, Niagara Falls.

THE EFFECT OF ROTATORY STIMULATION ON THE MOVEMENTS OF THE HEAD AND EYES IN NEWBORN AND YOUNG KITTENS. MURLAND W. FISH and WILLIAM F. WINDLE, J. Comp. Neurol. **54**:103 (Feb.) 1932.

Although the labyrinthine mechanism is sufficiently developed at birth to enable the kitten to right itself, which is necessary before it can crawl to the mother, it is probably immature; other vestibular reflexes do not appear until a later time. In the present study the postnatal development of vestibular function has been followed, and particular attention has been given to the ocular reactions which occur in response to rotatory stimulation.

Nine litters of kittens (thirty-nine animals), all of which were born in the laboratory, were examined; also several fetal kittens which were a week or less from term. One or both eyes were opened surgically by a slit in the palpebral membrane with a sharp knife on the day of the first observation, which was always on or before the third day after birth. Stimulation of the vestibular apparatus was accomplished by rotating the animals about the dorsoventral axis. Postrotatory nystagmus was looked for at the cessation of eight or ten rotations on a turntable, operated at about one turn per second. Other reactions of the animal, such as deviation of the head, were observed during and after rotation on the turntable.

The rotatory and postrotatory reactions appeared at the same time. Nystagmus was present in more than 75 per cent of the kittens on which operation was performed between the fifth and seventh days after birth. Deviation and irregular oscillating movements of the eyes appear a day or two before nystagmus, but some time later than deviation of the head, following rotatory stimulation. The nystagmus observed in young kittens is slow and follows a latent period. Characteristic adult responses appear before the end of the third week of life.

FRASER, Philadelphia.

THE EFFECT OF CEREBRAL DESTRUCTION ON REASONING AND LEARNING IN RATS. NORMAN R. F. MAIER, J. Comp. Neurol. **54**:45 (Feb.) 1932.

The purpose of this experiment was: (1) to isolate two possible types of behavior integrations and (2) to investigate the effect of cortical lesions on each of these abilities. The types of integrations examined were: (*a*) those formed by the spontaneous coming together of the essential of two isolated experiences and involving R (reasoning), and (*b*) those formed by the combining of two contiguous experiences and involving ability L (learning). Tests for reasoning, for reasoning plus learning and for reasoning minus learning were given. All rats were given at least six days' training on running narrow pathways. Then three days were given to preliminary tests. Male and female rats, ranging from 200 to 400 days of age, were used. Thirty-four were operated on and 23 were used for controls. The operation consisted of destruction of different amounts of cortical tissue in the frontal half of both hemispheres by means of thermocautery. Work was not begun with them until three weeks after the operation.

The author reports that abilities R and L were both found in the rat. Ability R was profoundly affected when the extent of destruction exceeded 18 per cent of the exposed surface of the brain, but ability L was not affected by lesions as great as 40 per cent. Because the lesion which affected R did not affect L, the author concludes that R and L are qualitatively different. Rats on which operation was performed showed a much greater tendency to repeat errors than did normal rats.

The author interprets ability R to be the ability which makes it possible to organize past experiences in terms of a goal or an end, and ability L to be the ability to organize past experiences in the order in which they were experienced. The latter, he states, is reproductive in nature and makes for stereotyped behavior, whereas ability R makes for new and original types of behavior.

ADDISON, Philadelphia.

ECONOMIC READJUSTMENT FOLLOWING HEAD INJURIES. TEMPLE FAY, Surg., Gynec. & Obst. **54**: 362 (Feb. No. 2A) 1932.

In cases of head injury, the gnostic areas of the brain, receiving five times the blood supply of the basal vital areas, suffer proportionately from edema. The fluid collecting over the frontal areas forms a hydraulic cast, producing pressure atrophy as definitely as a plaster cast around a swollen arm. Most of the psychic sequelae to head injuries are due to this mechanism. The problem of preventing the atrophy resolves itself into an attempt to maintain optimum cerebral circulation by subtracting from the cranial contents a volume of its least important component—the cerebrospinal fluid. To this end, Fay recommends the following program: On admission, the patient receives intravenously 50 cc. of 50 per cent dextrose, followed by complete spinal drainage, repeated every six hours if necessary. Hydragogs, such as magnesium sulphate, are administered both orally and per rectum. For the first two weeks, the patient's intake of fluids is restricted to a total of 30 ounces (887.1 cc.) of liquid per day; after discharge from the hospital, a dehydration regimen is continued, with the intake of fluids never totaling more than 1 quart daily.

Early decompression, Fay insists, is not justified. Hernia and laceration are almost certain to follow this insult to the cranium. Decompression never succeeds when dehydration fails. If signs of focal pressure have established the presence of a subdural or epidural hemorrhage, surgical intervention is necessary; and if the fracture of the skull is comminuted, débridement is required, but otherwise no operative intervention should be performed on the injured skull. The success of this therapy is exemplified by tables and the mechanism made clear by diagrams and illustrations drawn by Fay himself.

DAVIDSON, Newark, N. J.

SENILE DEMENTIA PARALYTICA. U. DE GIACOMO, Riv. di pat. nerv. **40**:308 (July-Aug.) 1932.

De Giacomo describes a case of dementia paralytica which developed at the age of 70 and in the early stages of which a diagnosis of cerebral arteriosclerosis was made. The diagnosis was confirmed by histologic studies of the nervous system. Interest in the case lies in the fact that there was an association of arteriosclerotic and senile changes with dementia paralytica. Solomon, in 1921, reported a similar observation. From a survey of the literature, de Giacomo proposes the following types of senile dementia paralytica: (*a*) a definite association between lesions of dementia paralytica and of senile dementia; (*b*) lesions of dementia paralytica alone; (*c*) intermediary forms in which lesions of both conditions are intermingled, with those of one or the other more or less dominant.

Clinically, the mental symptoms, even in the purest cases of senile dementia paralytica, are somewhat different from those occurring in earlier periods of life, for the following reasons: (*a*) Senile dementia paralytica is the result of an abnormally long latent period of the syphilitic involvement of the nervous system in relation with individual and constitutional factors, as a result of which there will be a slighter development of the delirium; (*b*) the process of dementia paralytica in old people cannot take a stormy course because of the diminished activity of the senile organism, which in histopathologic terms means that inflammatory reactions are much less conspicuous; (*c*) senile mental processes have fundamentally a tendency toward affective depression instead of euphoria.

Therapeutically, the author advocates malarial treatment and gives as contraindications only debility and undernourishment resulting from advanced age.

FERRARO, New York.

SPINAL FLUID IN SYPHILIS: II. A COMPARATIVE STUDY OF 522 SPINAL FLUIDS BY COMPLEMENT-FIXATION AND MICROSCOPIC SLIDE PRECIPITATION TESTS; A PRELIMINARY REPORT. LEO SPIEGEL, JOSEPH ELLER and CHARLES REIN, Arch. Dermat. & Syph. **26**:819 (Nov.) 1932.

Five hundred and twenty-two specimens of cerebrospinal fluid withdrawn by cisternal puncture from 317 patients were examined by both the Wassermann test and the slide precipitation test of Kline and Rein. In a group of 171 examinations there were ten discrepancies: two patients showed a positive complement-fixation reaction and a negative reaction with the slide test, while in eight these findings were reversed. As all the patients gave clinical evidence of neurosyphilis, it would appear that the slide test was the more sensitive. A similar comparison was made in a group of eighty patients who were known to have syphilis of the central nervous system. In only one case did the slide test fail to verify the diagnosis; on the other hand, in sixteen instances a negative Wassermann reaction was obtained in the face of a positive reaction with the slide precipitation test. Of a group of seventy-one patients under treatment for tabes or dementia paralytica, three showed a negative reaction with the slide test and a positive reaction with the complement-fixation test, while forty-four showed a negative Wassermann and a positive reaction with the Kline and Rein test. This illustrates the persistency with which the reaction with the slide test remains positive in patients undergoing therapy who show negative reactions with all other tests. The authors' conclusion is that the slide precipitation reaction is much more sensitive than the complement-fixation reaction. They advise that both these tests be utilized in serologic diagnosis of the spinal fluid and that the total protein content and globulin content be determined as well.

DAVIDSON, Newark, N. J.

ANATOMIC TYPES OF GLIOMA OF THE BRAIN. P. SCHWARTZ, Nervenarzt **5**:449 (Sept. 15) 1932.

Schwartz expresses the opinion, based on an anatomic study of four hundred cases of intracranial tumor, that intracerebral neoplasms like meningiomas show

a predilection for certain areas. He has been able to classify his material on gliomas into definite groups, the tumors in each group, though different histologically, being practically identical as regards point of origin, mode of extension and general contour. The present contribution is limited to cases in which the growth had invaded the cortex. Tumors of the anterior superior callosohemispheric angle, which arise in the angle between the superior surface of the corpus callosum and the medial surface of the hemisphere, are divided into four subgroups, largely according to the cortical areas involved. The extension of all tumors in this group is limited inferiorly by the lateral prolongation of callosal fibers into the corona radiata. None of the foregoing (and of two other types of neoplasm of the frontal lobe, tumors of the inferior and middle frontal convolutions, respectively, only the latter) invade the frontal pole. A fourth type, which has its origin below the knee of the corpus callosum, extends back into the gray matter of the hypothalamus and across the midline into the opposite hemisphere. Five types of tumor of the temporal lobe are presented, i. e., tumors of the superior, middle and inferior temporal gyri and tumors of the fusiform and hippocampal gyri.

With further experience Schwartz hopes to be able in every case to predict, from the area of the cortex involved, the location and the extent of the infiltrating process in the deeper structures. So far he has been successful in this respect. His experience to date also permits the hope that it may be possible to classify the various types of glioma clinically as well as anatomically.

DANIELS, Denver.

IS RETINITIS PIGMENTOSA DUE TO VITAMIN DEFICIENCY? JOSEPH LEVINE, Arch. Ophth. **9**:453 (March) 1933.

This paper is an ophthalmologic review. It is of interest to the neurologist in that the pigmentary degeneration described is progressive, is considered as incurable and as leading to complete degeneration and occurs in the membrane of nerve tissue in as highly specialized a system as the retina. Levine discusses in detail the opinions expressed in the literature. His inferences, unfortunately, cannot be conclusive. He must agree with Angell, who stated in 1895, "We now and then find a temporary improvement in sight occurs, and that this is often supposed to result from treatment, but that such improvement comes and goes without treatment as well." From the contents of the review it may well be considered that retinitis pigmentosa is a disease due to a vitamin deficiency.

Some outstanding opinions relative to the etiologic factor are cited. Derby thought that the condition is due to consanguinity; Nettleship did not think so, while Webster and Bader thought that this factor plays a part. Wilmer believed that heredity plays the important rôle. Knapp considered only endarteritis obliterans. Collins thought that abiotrophy of the neuro-epithelium is the cause. Verhoeff said that one must look elsewhere for the etiologic factor; he believed that cirrhosis of the liver and jaundice, with its deleterious effects, might be responsible. Wolbach and Howe found that the most specific changes in tissues in vitamin A deficiency are degeneration and damage of epithelial structures. Fuchs and Uyemura described cases of idiopathic hemeralopia which cleared up under vitamin A therapy. It is interesting that, while differences of opinion exist as to the etiology, there is the conclusion that "once the disease is established the end-results are all the same."

SPAETH, Philadelphia.

THE ENCEPHALITIS OF DOGS WITH ECK FISTULA FED ON MEAT. JOSEPH BALÓ and BÉLA KORPÁSSY, Arch. Path. **13**:80 (Jan.) 1932.

Six of eight dogs with an Eck fistula, fed on a one-sided diet of meat, became ill, presenting symptoms of encephalitis. They were unable to transmit the encephalitis to dogs; that is, the intracerebral inoculation of brain material led to fatal gastric hemorrhages arising from erosions and ulcers caused by minimal lesions of the brain during intracerebral inoculation. No histologic evidence of

encephalitis was found in these dogs or in the rabbits inoculated. On the basis of these investigations, there is no evidence that the encephalitis of dogs with an Eck fistula is caused by a living micro-organism or by a virus. They regard the encephalitis occurring with the one-sided meat diet and intoxication was due to the exclusion of the liver. The intoxication may follow a periodic course. The intoxicated dog does not eat; following fasting, the toxic symptoms disappear, but they reappear after the dog again begins to eat meat. An intoxication of mild degree does not necessarily bring about histologic alterations in the brain. Such alterations usually follow the attacks of encephalitis, appearing at intervals. Fatal intoxication causes alterations in the brain corresponding to nonsuppurative encephalitis, which are localized in the caudate nucleus. The location of the encephalitis of dogs with an Eck fistula in the striate bodies again proves the relationship of abnormal liver function to the brain. The finding first pointed out in these experiments that the encephalitis of dogs with an Eck fistula is localized electively in the striate bodies brings a new prospect for the experimental study of the etiology of Wilson's disease and pseudosclerosis.

WINKELMAN, Philadelphia.

A CASE OF SKULL DEFORMITY RELATED TO THE SO-CALLED ACROCEPHALOSYNDACTYLIA. A. N. BRONFENBRENNER, Psychiat. Quart. **6**:612 (Oct.) 1932.

The prematurely born son of a thyrotoxic mother and an alcoholic father was admitted to the hospital because of defective speech and poor progress in school. During pregnancy the mother had suffered severely from inadequate diet and was threatened with eclampsia. The patient was born five weeks prematurely. At birth the child had an umbilical and inguinal hernia and an undescended testis. Teething, walking and talking were delayed. When the child was examined at the age of 6, he had a defect in speech, the essential elements of which were rhinolalia aperta and sigmatism. Although his deportment and appearance suggested backwardness, mental tests revealed a normal intelligence. The head was oxycephalic, i. e., disproportionately high and short, with the planes of the face and occiput converging from below upward. Roentgen examination revealed craniostenosis. There were spina bifida, prognathism of the lower jaw, uvula bifida and a congenital cardiac defect. The palate was bulky and short. The general developmental disorder, combined with the specific cranial defects, suggests a classification of the case as a form of acrocephalosyndactylia. Bronfenbrenner is inclined to believe that the mother's dietetic insufficiency during pregnancy produced changes in the chemical composition of the amniotic fluid, resulting in the developmental defects described. The outlook is not as hopeless as would appear from a cursory survey of the findings. Proper training will enable the boy to use his accessory muscles to compensate for the insufficiency of the palate, while plastic surgery may be employed to repair some of the bony and cartilaginous defects.

DAVIDSON, Newark, N. J.

A NOTE ON THE EFFECT OF REPEATED HYPNOTIC STIMULATION. O. H. MOWRER, J. Abnorm. & Social Psychol. **27**:60 (April-June) 1932.

The author discovered accidentally that a white leghorn rooster could, after being once subjected to a bright light such as is used for motion picture illumination, be hypnotized. The method of hypnosis was by stroking the comb and making passes before the eyes of the fowl. It was found that the literature had meager accounts of the effect of repeated hypnotization. Here seemed to be an excellent opportunity to observe such an effect. On eighteen successive days (with one exception) the fowl was hypnotized three times in rapid succession, and data were collected both as to the length of time required to effect the "trance" and the length of time during which the bird remained hypnotized. The results were as follows: The time required to accomplish the hypnosis remained practically the same throughout. At the end of thirty seconds of comb-stroking

the subject was lying inert on the ground. The duration of the trance, however, decreased in length of time from five minutes to zero by the end of the seventeenth day. There was a gradual diminution in the length of time the bird remained hypnotized. This diminution indicates that repeated hypnotization tends to desensitize rather than to sensitize the subject. It is claimed by the author that this is in agreement with similar experiments performed on human beings. It is remarked, however, that the attenuation of response after a repetition is at variance with the general law of habit formation and learning, in which response is always increased or stamped-in by repetition.

WISE, Howard, R. I.

DEVIATION OF THE BODY AND THE GAIT IN CEREBELLAR DISEASE. H. HOFF and O. PÖTZL, Jahrb. f. Psychiat. u. Neurol. **48**:217, 1932.

The authors report a case of cerebellar syndrome following apoplexy due to hypertension. Early in the disease there were forced rotation to the right (with the body in the upright position) and, later, deviation of the head and body to the right while standing or walking. Only in this position were the equilibratory disturbances (vertigo and falling to the right) compensated for. Necropsy revealed a softening in the right cerebellar hemisphere limited exclusively to the white substance; the lesion extended laterad from the dentate nucleus, its greatest diameter being in the sagittal plane. The cerebellar cortex was intact, only a narrow zone in the most lateral portion of the dentate nucleus being somewhat affected. The clinical picture of cerebellar deviation in this case is attributed to the supranuclear softening in the right cerebellar hemisphere, in contrast to the usual clinical picture consisting predominantly of hypotonia, tremor, dysmetria and cerebellar ataxia of certain muscles of the upper extremities noted in cases of softening of the hilus of the dentate nucleus. In the case reported there was an interference with the function of the lateral portion of the right dentate nucleus, primary clinical manifestations of which were disturbances in equilibrium of the body toward the side of the lesion. These disturbances were evident only during gait, with the body in the upright position. They were otherwise analogous to the forced rotations of the body (rolling phenomena) observed in quadrupeds following hemicerebellar extirpation.

KESCHNER, New York.

AFFERENT FIBERS IN THE CERVICAL SYMPATHETIC TRUNK, SUPERIOR CERVICAL GANGLION AND INTERNAL CAROTID NERVE. DAVID A. CLEVELAND, J. Comp. Neurol. **54**:35 (Feb.) 1932.

This is a study to determine by degeneration experiments whether or not large sensory fibers pass from the cervical sympathetic trunk through the superior cervical ganglion to the internal carotid nerve. The sympathetic trunk was aseptically dissected out and a piece 0.5 cm. long removed midway between the superior cervical and stellate ganglia. In five cats the left trunk was cut and in five the right. The other trunk was left intact for control. Four animals were killed after eight days and six after fifty days. The cervical sympathetic trunk, superior cervical ganglion and the branches arising from the upper pole of the ganglion were dissected free and laid out on a glass slide. The material was prepared by the osmic or by the Marchi method and cut either longitudinally or transversely and mounted serially. Before each animal was killed the distal ends of both cervical trunks were dissected down to the stellate ganglion, and the animal was allowed to awaken from anesthesia. When fully awake the animal was tested for response to pain. Similar observations were made on the sectioned side at the time of operation. The author finds that: 1. The cervical sympathetic trunk contains almost exclusively small myelinated fibers which are preganglionic and degenerate toward the superior cervical ganglion. 2. The number of myelinated fibers above 5 microns in diameter is approximately the same on the normal side and on that on which operation has been performed.

ADDISON, Philadelphia.

FURTHER STUDIES ON INDIVIDUALLY ACQUIRED AUTOMATIC ASSOCIATED MOVEMENTS. R. M. BRICKNER and L. V. LYONS, Bull. Neurol. Inst., New York **2**:294 (July) 1932.

The authors have previously reported observations in a typical case of postencephalitic paralysis agitans which indicated (1) that the automatic associated movements might be divisible into two groups, one phyletically founded and the other individually acquired, and (2) that the former are seriously impaired in paralysis agitans, while the latter are not. The present paper is a continuation of the study of acquired automatic associated movements. Two cases of paralysis agitans and two cases of dystonia musculorum deformans are briefly reported to illustrate the preservation of highly skilled acquired automatic associated movements utilized in boxing, baseball, rope-jumping, bicycle riding and roller skating. Such motor ability was well preserved, although the performance of phyletic automatic associated movements, such as standing and walking, was seriously impaired. During the performance of acquired automatic associated movements the dystonic movements cease. It is believed that only the few complicated acts in which the subject was highly trained and which were extremely well learned prior to the onset of illness can be demonstrated. This preservation of ability to perform acquired automatic associated movements is considered as evidence of the existence of a neuronic system for acquired movements (neokinetic) distinct from the system for primitive movements (paleokinetic), which is probably integrated in some part or parts of the cerebral cortex.

KUBITSCHEK, St. Louis.

LEFT-FOOTEDNESS. G. STERN and E. SCHILF, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:41, 1932.

There have been few studies on left-footedness. It is known that high jumpers usually take off with the left foot, in order to get the right leg over the bar first. Football players usually kick with the right foot, and sliding on ice is usually done with the right foot forward. Stern and Schilf studied footedness in 7,000 school children, using football kicking and sliding as their tests. It was found that left-handed persons are in many cases also left-footed. Left-footedness in right-handed persons is less common, but occurs; thus, they slide with the left foot and kick a ball with the left.

Left-sidedness varied in different schools. In one school in which 435 children were enrolled there were 4.4 per cent left-handed, 6.2 per cent left-footed and 6.2 per cent left-footed and left-handed pupils. In another school among 368 children there were 1 per cent left-handed, 0.5 per cent left-footed and 1.9 per cent left-footed and left-handed pupils. Not all left-handed persons are left-footed. In one school, among 300 children, there were 15 who were left-handed, none of whom were left-footed. Pure left-footedness without left-handedness is not as frequent as left-handedness with right-footedness.

The incidence of left-handedness and of left-footedness was greater in the school for subnormal children, and left-sided children were more numerous in schools for the hard of hearing.

ALPERS, Philadelphia.

THE DOUBLE INNERVATION OF FISH MELANOPHORES. SYLVIA M. MILLS, J. Exper. Zool. **64**:231 (Nov. 5) 1932.

When nerves are cut in the tail fin of Fundulus, the areas which remain light when the fish is over a dark background, or dark when the fish is over a light one, do not always coincide. Differences in the denervated areas with respect to contracting and to expanding nerves are also demonstrated by the contraction due to electrical stimulation and the expansion following removal of this stimulus. Cases are reported of partly denervated areas in which the cells fail to contract on electrical stimulation of the central nervous system, but expand when the current is turned off. In other instances melanophores contracted with the current, but

failed to expand when it was turned off. Mechanical stimulation of melanophore nerves causes melanophore expansion. It is concluded that the melanophores of Fundulus have a double innervation.

Results obtained from electrical stimulation of the central nervous system following incisions in various parts of the tail indicate the course taken by melanophore nerves. The contracting fibers run parallel to the fin rays without sending branches into adjacent radials or interradials. The majority of melanophore-expanding fibers also run parallel to the rays, but lateral branches supply some cells in adjacent radials and interradials. In the distal third of the tail there is considerable lateral branching of both types of nerve.

WYMAN, Boston.

THE DEVELOPMENT OF THE VESTIBULAR RIGHTING REFLEX IN THE CAT. WILLIAM F. WINDLE and MURLAND W. FISH, J. Comp. Neurol. **54**:85 (Feb.) 1932.

This study has been made to determine the time when the vestibular mechanism begins to function and to correlate this with the early righting reaction of fetal kittens. A series of seventy-two fetal kittens was studied.

The criteria used to determine the presence or absence of vestibular function were: (1) the ability of the fetuses to right themselves from a flat surface was compared with their ability to orientate themselves in water beyond their depth; (2) they were rotated on a revolving stool at a rate of about one turn in two seconds and deviation of the head during and after rotation was recorded; (3) one or both labyrinths were destroyed and the effects on the righting reflex were studied; (4) in order to determine whether or not the righting reaction persisted after most of the afferent impulses from the body had been eliminated, the spinal cord was sectioned between the seventh cervical and second or third thoracic segments in one one day old and in three newly born kittens.

The vestibular righting reflex appears in kitten fetuses of from 100 to 115 mm. in crown-rump length (about the fifty-fourth day in a gestation period which may be sixty, or more, days long). The body righting reflex appears somewhat earlier, being present in fetuses 100 mm. long (about the fiftieth day).

ADDISON, Philadelphia.

STATE OF THE FLEXOR REFLEX IN PARAPLEGIC DOG AND MONKEY RESPECTIVELY. J. F. FULTON and C. S. SHERRINGTON, J. Physiol. **75**:17 (May) 1932.

There is a marked difference between the reflex activity obtained in the paraplegic dog or cat and that obtained in the paraplegic monkey. The flexor reflex of the hindlimbs in the dog and cat whose spinal cord has been transected there is facile and vigorous, while in the monkey whose cord has been transected there is difficulty in evoking it or failure to evoke it. This diversity is important, because it is evidently correlated with the relative distances respectively separating these two mammalian types from man. Using the tibialis anticus, the authors attempted to find a numerical expression for the diversity of the flexor reflex by two groups of experiments: (1) in which the myographic examination was made three or four hours after spinal transection, and (2) in which it was made not earlier than the twenty-first day after transection.

It was found in the monkey, after spinal transection in the thoracic region, that the flexor reflex of the hindlimbs, instead of being facile and vigorous as in the dog and cat, is for a time unobtainable or, if obtainable, is very weak. In the course of several weeks there ensues, as in the dog and cat, a slight increase of the reflex; the reflex can become distinctly elicitable, but a condition of masking and deterioration of the nerve-muscle response (isolation dystrophy) supervenes, which tends to obscure observation of whatever central reflex action exists by impairing its means of expression.

ALPERS, Philadelphia.

INTRAMEDULLARY COURSE OF THE DORSAL-ROOT FIBERS OF THE FIRST THREE CERVICAL NERVES. S. W. RANSON, HELEN K. DAVENPORT and E. A. DOLES, J. Comp. Neurol. **54**:1 (Feb.) 1932.

The intramedullary courses of the dorsal root fibers of the first three cervical nerves were studied in Marchi preparations in four cats. After bilateral section of these nerves the animals were allowed to live for from fifteen to twenty-one days. The distribution of these fibers is shown in ten illustrations. The descending branches are short, turn in the lateral part of the cuneate fasciculus and can be traced downward for a distance of two segments. In the medulla the ascending branches occupy the lateral part of the cuneate fasciculus. Many of them end in the accessory cuneate nucleus, but others can be traced as high as the rootlets of the glossopharyngeal nerve. These form one of the constituents of the medial part of the restiform body. In the medulla also fine fibers can be traced medialward from the fasciculus cuneatus to the upward continuation of the intermediate nucleus, which lies posterolateral to the hypoglossal nucleus. Other coarser fibers accompany these fine fibers as far as the tractus solitarius and its nucleus, within which they appear to end. In the spinal cord the most conspicuous group of collaterals goes to the intermediate nucleus of Cajal, which is situated lateral to the central gray matter. Others are distributed through the anterior and posterior gray columns and a few cross in the posterior commissure. The observations of these authors support Cajal's contention that spinal-nerve sensory collaterals may end directly on motor neurons, producing a two-neuron reflex arc.

ADDISON, Philadelphia.

ANATOMICOCLINICAL STUDY OF POSTTRAUMATIC NASAL CAUSALGIA WITH PUPILLARY DISTURBANCES. J. CREYSSEL and P. MOUNIER-KUHN, Rev. d'oto-neuro-opht. **10**:663 (Nov.) 1932.

A man, aged 33, suffered a severe wound of the left side of the nose and face. Following the accident there developed a painful vasomotor and secretory syndrome, with nasal pain, tumefaction and congestion, obstruction and rhinorrhea, appearing in crises from various causes, principally exposure to cold; a syndrome of alternating vasodilatation in the turbinates of each side of the nose, with concomitant pupillary modifications—mydriasis on the side of the vasoconstriction and myosis on the vasodilated side, and, later, a typical causalgic syndrome, with violent superficial pain, occurring by crises after the least touch on the nose and relieved by pressure. The scar, at first normal, became edematous with a white spot in the middle, which was hypersensitive and seemed to be the center for neuralgic radiations. After the cicatrix and the middle turbinate body had been removed and the nose had been treated, the symptoms disappeared. Histologic examination of the excised scar did not reveal manifest nerve lesions. The explanation of the symptoms therefore rests on vasomotor disturbances that brought about in the fibrous tissue intermittent compression of the nerve filaments in a richly innervated area. Therapy consists in removing the irritating focus and, if necessary, the superior cervical sympathetic ganglion.

DENNIS, Colorado Springs, Colo.

SYPHILITIC ACUTE ANTERIOR POLIOMYELITIS. WILLIAM W. CHRISMAN, Am. J. Syph. **16**:308 (July) 1932.

Only seven cases of acute anterior poliomyelitis demonstrably due to syphilis have been found in a review of the literature by Chrisman. He adds to this scanty collection an eighth case. His patient was a white man, aged 24, who became feverish and noticed weakness in the knees, accompanied by chills and headache. Within two days a complete flaccid palsy of the legs had developed. There were no sensory changes. The spinal fluid gave a four plus Wassermann reaction, a colloidal mastic curve of 4553210000 and a strongly positive globulin precipitation. The fever subsided within a few days. In spite of intensive treatment, including spinal drainages, intravenous injections of neoarsphenamine and bismuth therapy,

improvement was slow and inadequate. Within ten weeks, atrophy of the legs, thighs and buttocks was noted, and a reaction of degeneration was obtained. A year later, the patient left the hospital with no further function in the legs. The failure of the antisyphilitic preparations to improve the poliomyelitis is to be expected, because of the actual destruction of anterior horn cells which must have taken place. It is probable that these degenerations were preceded by vascular changes and do not represent the direct effect of the syphilitic process on the ganglion cells.

DAVIDSON, Newark, N. J.

THREE CASES OF TUMORS IN THE POSTERIOR CRANIAL FOSSA WITH MENTAL SYMPTOMS. R. W. SOUTHERLAND, Bull. Neurol. Inst., New York **2**:144 (March) 1932.

In a series of 128 cases of tumors in the posterior cranial fossa, three were found which showed a marked degree of intellectual deterioration and mental impairment. The clinical histories in these cases are given in detail. In the first case cited, that of a woman, aged 54, the mental symptoms were outstanding and preceded for some months localizing neurologic signs. In the other two cases the mental symptoms were somewhat less prominent but still sufficiently pronounced to confuse in diagnosis. All three cases presented the difficulty of differentiating between a lesion in the frontal lobe and one in the posterior cranial fossa. Ventriculograms in each case gave the information necessary for correct diagnosis. The author reviews briefly some of the literature pertaining to the localizing value of mental symptoms in tumors of the brain and cites a number of cases reported by others in which mental disturbances were prominent with neoplasms in the interior fossa. While mental symptoms may be produced during the process of disturbances due to tumors in the posterior fossa, the author states that he was unable to find any case in which subtentorial growth in an infant or an adolescent child had produced such disturbance.

KUBITSCHEK, St. Louis.

EVIDENCE FOR A NEUROHUMORAL CONTROL OF FISH MELANOPHORES. SYLVIA M. MILLS, J. Exper. Zool. **64**:245 (Nov. 5) 1932.

The responses of melanophores of Fundulus in a denervated area following a change in the shade of the fish do not take place simultaneously. They start at the periphery of the denervated area and are gradually transmitted to its center. This indicates that secretions affecting melanophores are not produced in a distinct gland and carried in the blood stream, but rather that they are formed in the surrounding tissues and reach the denervated cells by gradual spread. The reactions of innervated cells to artificial stimulation are more rapid than the normal background reflex. Denervated cells surrounded by melanophores which are reacting to mechanical or electrical stimulation react in the same way as the innervated cells, though more slowly. They also change much more rapidly under these circumstances than when responding to the shade of the background. Reactions of denervated melanophores, when the surrounding innervated cells respond to artificial stimulation, also occur in tails isolated from the body by a cut posterior to the anal fin. They cannot, therefore, be caused by secretions from glands anterior to this cut, and distributed in the blood stream. These results are consistent with the theory that melanophore nerve endings secrete substances so near the cells they supply as to cause them to react. These secretions are thought to be responsible for the reactions of denervated melanophores, which they reach by transfusion.

WYMAN, Boston.

TUBERO-INFUNDIBULAR SYNDROME. A. OBREGIA, A. DIMOLESCO and S. CONSTANTINESCO, Encéphale **27**:93 (Feb.) 1932.

A detailed case history is presented. A tumor of the third ventricle, of extraventricular origin, occurring in a man, aged 53, is described, and a pathologic interpretation is made. The signs and symptoms were: bitemporal hemianopia

resulting from a lesion of the internal fibers of the optic chiasm, and optic atrophy from pressure on the chiasm; dysarthria, probably resulting from irritation of the fibers in the foot of the peduncle at the upper level of the fifth nerve. Hypothermia of tuber cinereum origin is well known through many citations in the literature. This is also true of glycosuria, although in this case there was no associated hyperglycemia. Polydipsia, polyuria and polyphagia are presumably associated with the disturbance in carbohydrate metabolism and are recognized accompaniments of the syndrome. Loss of sexual capacity is undoubtedly due to adiposogenitalism. Hypersomnia is characteristic and is essentially the same as that so well known in encephalitis or other involvements of the region of the third ventricle. Mental disturbances are complex, representing alterations in thought, emotion and volition. It is not possible to describe a characteristic mental state or to correlate the particular state with the pathologic condition of the brain.

ANDERSON, Los Angeles.

INHERENT HEALING PROPERTIES OF ABSCESS OF THE BRAIN. JOSEPH H. GLOBUS and WALTER L. HORN, Arch. Otolaryng. **16**:603 (Nov.) 1932.

The authors state that the diagnosis and the exact location of abscess of the brain are easy; that the difficulty is in deciding what to do. They point out that there is a natural tendency to heal, as shown by encapsulation, which in time in some cases causes spontaneous recovery. They call attention to the fact that an abscess in the silent area more often results in recovery because encapsulation has become further advanced. The problem, then, is to know when an abscess is ready to be opened. When the abscess is in a part of the brain where its size or location causes interference with function which may be fatal, methods should be used to reduce the size temporarily, while one awaits complete encapsulation with subsequent shrinking of the scar. Therefore, the most important surgical indication is to establish and maintain "normal intracranial tension until the encapsulation is sufficiently advanced to permit of a more adequate and if need be more radical surgical procedure." It is important to know when the encapsulation is complete. Fifteen cases are reported. The authors commend the method of Dandy for use in supratentorial cases.

HUNTER, Philadelphia.

FACIAL DIPLEGIA IN POLYNEURONITIS. GEORGE WILSON and HAROLD F. ROBERTSON, Am. J. M. Sc. **183**:680 (May) 1932.

In a review of the literature of polyneuritis with facial diplegia, comment is made that, while extensive studies were completed of the central nervous system, comparatively little attention was paid to the peripheral nerves. Three cases are described. Case 1 occurred in a girl, aged 17, in whom, following a cold and sinusitis, double facial palsy, complete paralysis of the palate, paralysis of the left vocal cord and weakness of the right vocal cord, with polyneuritis developed. It was thought that the cranial nerve palsies were central in origin. Case 2 was that of a woman, aged 41, in whom polyneuritis and double facial paralysis developed ten weeks after childbirth, which was normal. Etiologic factors of dental infection and gonorrhea were found, and the nerve lesions were mostly peripheral in nature. Case 3 was that of a colored woman, aged 23, with more serious involvement than occurred in the two preceding cases; gradual improvement ensued in the three years following removal of septic tonsils. In view of the confusion in the nomenclature of this disease, the term neuronitis is suggested as the most descriptive.

MICHAELS, Boston.

ADHESIVE CHRONIC SPINAL PACHYMENINGITIS AND LEPTOMENINGITIS FOLLOWING MELITOCOCCIC MENINGITIS. G. NOTO, Riv. di pat. nerv. **40**:440 (Sept.-Oct.) 1932.

Noto describes a case of chronic adhesive pachyleptomeningitis following infection with Micrococcus melitensis of Bruce. Clinically, a compression syndrome of the spinal cord at the level of the seventh or eighth dorsal vertebra resulted. At

autopsy there was thickening of all the spinal meninges from the occipital foramen to the seventh or eighth dorsal vertebra. Histologically, the spinal cord at the level of the meningeal lesion disclosed only slight rarefaction of myelin sheaths in the marginal areas. The author reviews the complications of Malta fever and adds to those already known circumscribed spinal meningitis of which he claims this is the first report in the literature. He summarizes modern views on chronic leptomeningitis and their differentiation from extramedullary tumors. He calls attention to the contraindications for surgical procedures when the adhesions are extensive and insists on the necessity of establishing in circumscribed spinal arachnoiditis not only the superior but also the inferior level of the lesion.

FERRARO, New York.

NOTE ON THE SYMPATHETIC NERVE SUPPLY OF THE EYE IN THE CAT. EDWIN M. DEERY, Bull. Neurol. Inst., New York **2**:134 (March) 1932.

Because of increasing evidence of neural mechanisms within the eye, some of which can act independently of all connections with the central nervous system, the author studied the autonomic cells that migrate into the developing eye of the cat. A constant migration of neuro-ectodermal elements, which ultimately entered the eyeball, was found between the 8 and 15 mm. stage in cat embryos. The immedate origin of such cells was the ciliary ganglion anlage and the region of the ophthalmic artery. Morphologically, they seem identical with the migrating cells which in earlier stages produce the formation of the ciliary ganglion anlage. The greater portion of the migrating cells follow pathways provided by the short ciliary nerves and the optic nerve. A smaller portion move peripherally across the mesenchyme and enter the posterior surface of the eyeball over a wide arc. A small number enter the extra-ocular muscle anlages and remain there. These migrating cells are undifferentiated elements of neuro-ectodermal origin, and it is probable that they differentiate into neuroblasts within the eye.

KUBITSCHEK, St. Louis.

THE RANGE OF EFFECTIVE IODINE DOSAGE IN EXOPHTHALMIC GOITER: IV. THE EFFECT ON BASAL METABOLISM OF THE DAILY ADMINISTRATION OF ABOUT 0.75 MG. OF IODINE. WILLARD OWEN THOMPSON, PHEBE K. THOMPSON and ARCHIBALD C. COHEN, Arch. Int. Med. **49**:199 (Feb.) 1932.

This study was conducted on twelve patients suffering from exophthalmic goiter. After the metabolic rates at rest had become stationary, they received daily one drop of 12.5 per cent dilution of compound solution of iodine. This represents about 0.75 mg. of iodine daily. Four of the patients showed a reduction greater than 10 points in the metabolism rate—that is, 33 per cent showed definite improvement. From previous studies the authors knew that 88 per cent of patients receiving 6 mg. of iodine daily showed a fall in metabolic rate in excess of 10 points. Daily amounts in excess of 6 mg. of iodine were no more effective, while dosages of less than 0.75 mg. daily produced no certain effect. Therefore, the range of effective iodine dosage in exophthalmic goiter appears to lie between 0.75 and 6.0 mg. daily. Within these limits the metabolic rate would fall more or less in proportion to the amount of iodine absorbed.

DAVIDSON, Newark, N. J.

A CLINICAL AND PATHOLOGICO-ANATOMIC CONTRIBUTION TO THE CLONIC, RHYTHMIC CONTRACTIONS OF THE PHARYNGEAL MUSCULATURE. SCHMITT, Nervenarzt **5**:456 (Sept. 15) 1932.

After considering the clinical features of clonic, rhythmic contractions of the pharynx, Schmitt enumerates the lesions found at autopsy in previously reported cases. He is particularly impressed with the finding, in some cases of unilateral spasm, of a lesion in or lateral to the dentate nucleus on the same side, with an

associated atrophy of the corresponding brachium conjunctivum and the opposite red nucleus and inferior olive. In the case here reported, the findings were suggestive of a left cerebellar lesion when the patient was first seen. On reexamination three months later, very rapid rhythmic movements were seen in the left soft palate and left faucial pillars, as well as in the musculature of the left side of the pharynx. Nothing was found on exploration of the posterior cranial fossa two months after this, but at the time of a second surgical attack nearly a year after the patient was first seen, a large mass of neoplastic tissue was removed from the left cerebellar hemisphere. The patient died, and at autopsy no changes were found in either the right cerebellar hemisphere or in the basal nuclei, pons or medulla oblongata.

DANIELS, Denver.

THE FUNCTION OF THE BRAIN IN AUDITION. L. E. WILEY, J. Comp. Neurol. **54**:109 (Feb.) 1932.

This study was undertaken to determine what part (or parts) of the cerebral cortex is used in the formation and retention of an auditory habit and also to gain some knowledge of the functioning of the auditory mechanism. Rats were first trained to an auditory stimulus and then subjected to cortical operation. The lesions varied in locus and extent, covering practically the entire neopallium and involving from 2.6 per cent to 31.7 per cent of the total neopallial cortex. Ten days after operation, the rats were returned for study and retrained until they again reached the original criterion of learning. They were then killed; the brains were removed and sections were made to determine the place and extent of the lesion.

The results show that Fortuyn's area *p*, which includes the posterolateral part of the cerebral cortex, delimits the auditory mechanism fairly closely. Large destruction of area *p* may abolish an auditory habit, but the habit may be reacquired. The data show that there is a relationship between the extent of the destruction and the degree of postoperative amnesia.

FRASER, Philadelphia.

SYNDROME OF STEWART-MOREL: INTERNAL FRONTAL HYPEROSTOSIS WITH ADIPOSITY AND MENTAL DISTURBANCES. PAUL SCHIFF and J. O. TRELLES, Encéphale **26**:769 (Dec.) 1931.

The case reported is that of a man who, following a cranial trauma, was shown by roentgenogram to have frontal hyperostoses. Mental symptoms included intellectual retardation with depression and anxiety, changes in disposition and character and a neurotic picture. Neurologic symptoms and signs were continuous headache, with paroxysmal recrudescence, disturbances of equilibrium and walking; obesity of hypophyseal type, and altered genitalia. Studies of the blood showed hypercalcemia and some change in hydrogen ion concentration toward the acid side. In the literature most cases have been in women (85 per cent). There appears to be a primary lesion of the infundibulum of traumatic origin, resulting in disturbed metabolism of fat and of calcium. This case is the third in which a diagnosis was made ante mortem; the other two were reported by Morel and by van Bogaert.

ANDERSON, Los Angeles.

EQUILIBRIUM BETWEEN CEREBROSPINAL FLUID AND BLOOD PLASMA: V. OSMOTIC PRESSURE (FREEZING POINT DEPRESSION) OF HUMAN CEREBROSPINAL FLUID AND BLOOD SERUM. FRANK FREMONT-SMITH, GILES W. THOMAS, MARY ELIZABETH DAILEY and MARGARET P. CARROLL, Brain **54**:303 (Sept.) 1931.

Comparative freezing point determinations on simultaneous samples of blood serum and cerebrospinal fluid in ninety-four instances (on seventy-three patients) are reported. In forty-four of the seventy-one comparative determinations in nonmeningitic cases, the freezing point of the cerebrospinal fluid was the same as that of the serum within 0.005 C., confirming the views of Mestrezat and

Teschler. In ten instances of meningitis, the freezing point difference between the blood serum and the cerebrospinal fluid was greater than 0.025 C. This evidence helps to corroborate the thesis that the cerebrospinal fluid is a dialysate in osmotic equilibrium with the blood plasma.

MICHAELS, Boston.

RECURRENCE OF ATTACKS IN MANIC-DEPRESSIVE PSYCHOSES. HORATIO POLLOCK, Am. J. Psychiat. **11**:567 (Nov.) 1931.

An analysis of the data on the subject in the New York Department of Mental Hygiene leads Pollock to believe that the likelihood of recurrence of an attack of manic-depressive psychosis has been overemphasized. He thinks that 56 per cent of the males and 58 per cent of the females have had only a single attack; depressions are even less likely to recur than manias, as in not more than 42 per cent of the cases of melancholia was rehospitalization necessary. Patients less than 40 and more than 20 years of age at the time of the first admission had fewer recurrences than older or younger persons. The duration of each paroxysm varies, increasing somewhat irregularly with age. For persons under 30 the average duration was from eight to ten months; for the whole group, the average duration of each attack was from fifty to sixty weeks.

DAVIDSON, Newark, N. J.

THERAPEUTIC USE OF ANTIPOLIOMYELITIS SERUM IN PREPARALYTIC CASES OF POLIOMYELITIS. WILLIAM H. PARK, J. A. M. A. **99**:1050 (Sept. 24) 1932.

The results of observations made by Park on treated and untreated patients in the preparalytic stage of poliomyelitis during the 1931 outbreak do not give any statistical proof that the serum has any value when given in cases after the cells of the central nervous system are involved. The fact that the report of Kramer, Aycock and their co-workers, which also deals with patients treated with serum and those not treated, gives similar results is of great importance. Nevertheless, the uniformly optimistic opinions of those who have not observed untreated patients for a comparison cannot be entirely disregarded. The author believes that in the future it could be arranged to have both the treated and the untreated patients observed by impartial judges so that a final correct judgment might be formed and generally accepted.

EDITOR'S ABSTRACT.

SYMPATHETIC ACTIVITY IN CERTAIN DISEASES, ESPECIALLY THOSE OF THE PERIPHERAL CIRCULATION. W. J. MERLE SCOTT and JOHN J. MORTON, Arch. Int. Med. **48**: 1065 (Dec.) 1931.

To distinguish vascular spasm from vascular occlusion, the authors offer a test requiring nerve-block anesthesia. The temperature of the skin peripherally is noted before and after the injection of the anesthetic; if it remains the same in both instances, occlusion without spasm is present. If injection of the anesthetic is followed by an increase in the peripheral temperature, this increase is compared with standards. If the postanesthetic temperature is the same as in the standard, the patient's circulatory symptoms are due to spasm. A rise in temperature falling short of the standard is an index of occlusion and spasm combined. The anesthetic used is procaine hydrochloride.

DAVIDSON, Newark, N. J.

MALARIAL THERAPY IN SCHIZOPHRENIA. G. BELLONI, Riv. di pat. nerv. **37**:508 (March-April) 1931.

Belloni discusses the literature on malarial therapy in schizophrenia, including about twenty articles from European countries and the United States. He adds his personal experiences with eighteen patients treated by the same procedure. In his own material he reports six cases of complete, and four of partial, remission.

Of the six favorably influenced, five cases belonged to the hebephrenic, and one to the catatonic, type of dementia praecox. All were early cases, the oldest having existed for eighteen months. From his own material and a critical review of previous results the author reaches the conclusion that malarial treatment is worth while in schizophrenia, and that the attitude of some authors against this therapy is not justified.

FERRARO, New York.

MORTALITY FROM ABSCESS OF BRAIN. FRANCIS C. GRANT, J. A. M. A. **99**:550 (Aug. 13) 1932.

On the basis of his observations in fifty-one verified cases of abscess of the brain, Grant makes an attempt to determine the influence on the mortality from this condition of the following factors: difficulty in diagnosis and localization, time of treatment and method of treatment. His conclusions are as follows: 1. Brain abscess is not more difficult to diagnose and localize than any other intracranial lesion, provided sufficient care is taken in the study of the case. 2. An abscess of the brain should not be drained until it seems certain that encapsulation has occurred, preferably in the sixth week after the onset of symptoms. 3. Drainage by a small rubber tube has given satisfactory results. No matter what method is used, unnecessary trauma to surrounding tissue is to be scrupulously avoided.

EDITOR'S ABSTRACT.

THE VALUE OF PSYCHOLOGICAL TRAINING IN ORGANIC DISEASE. CAVENDISH MOXON, Ment. Hyg. **15**:751 (Oct.) 1931.

Preferring the term "personality training" or "psychological training" to "psychotherapy," Moxon suggests that it should be used more widely in organic medicine. Even a broken leg, he thinks, will heal better if the psychic situation is properly handled. (In this he quotes Groddeck.) To the end that there may be an ample supply of practitioners of psychotherapy, nonmedical psychologists should be recognized by physicians and called on more frequently for consultation and treatment. By transferring these duties from the physician to the layman, the already overcrowded medical curriculum will, Moxon altruistically hopes, be relieved, and the neuropsychiatrist will thus be free to devote himself to the organic side of his specialty.

DAVIDSON, Newark, N. J.

THE HEART IN MYOTONIA ATROPHICA. G. GUILLAIN and L. ROUQUÈS, Ann. de méd. **31**:158, 1932.

The simultaneous occurrence of disease of striated and heart muscles, which is found in the progressive muscular dystrophies, could not be demonstrated pathologically in cases of myotonia atrophica. Clinically, there were no striking changes in blood pressure. The electrocardiogram revealed in four cases mild deviations from the normal, which appear more significant in the light of other publications of more marked arrhythmias occurring in this disease.

MYOTONIA ATROPHICA AND PARATHYROID INSUFFICIENCY. L. ROUQUÈS, Ann. de méd. **31**:167, 1932.

The hypothesis that disease of the parathyroid glands is the primary etiologic factor in myotonia atrophica is not supported by a careful analysis of the clinical symptoms and laboratory findings. The author is in favor of Curschmann's idea that pluriglandular and muscular disturbances are the common expression of a disease of the central nuclei of the sympathetic nervous system.

WEIL, Chicago.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, April 28, 1933

A. C. Buckley, M.D., *President, in the Chair*

Basophil Adenoma of the Pituitary Body. Dr. B. J. Alpers.

This article will be published in full elsewhere.

Experimental Production of Abscess of the Brain in Cats. Dr. Robert A. Groff.

The object of this report is to detail a method for the experimental production of abscess of the brain in cats. The work was performed at the Laboratories of Research Surgery and Neurosurgery, University of Pennsylvania Medical School, Philadelphia. The ultimate aim is to trace the pathologic development of abscesses of the brain and later to evaluate the various methods of surgical treatment.

The problem has been approached along two lines: 1. The infecting agent was indirectly implanted into the brains. An attempt was made to induce an infected thrombus in one of the smaller arteries of the brain by the injection of bacteria into the carotid artery. Various strains of staphylococci and hemolytic streptococci were used. The organisms were introduced either in a plain broth culture, in pus or in broth cultures to which had been added small organic particles. Numerous unsuccessful attempts were made by my predecessor, Dr. Hugh Stewart, to produce abscesses in this way. Because a lesion resulting from such experiments would be extremely difficult to localize, and because one aspect of the problem was to study the abscesses from the standpoint of treatment, this first method was temporarily abandoned.

2. The bacteria were directly implanted into the brain substance. The surgical technic employed was essentially the same for all of the experiments. It was soon evident that a two-stage operation was imperative in order to prevent meningitis. The first procedure consisted merely in exposing the bone beneath the temporal muscle and in making a cranial defect not larger than 3 or 4 mm. in diameter. The exposed dura and the underlying cortex were then punctured with a needle in numerous places for the purpose of producing a reaction which would result in obliteration of the subarachnoid space at this point. The muscle and skin were sutured separately, and the animal was allowed to recover for a period of three or four days. At the second operation, the wound was opened and the cranial defect exposed. A sterile needle was inserted through the dura diagonally into the brain substance for a distance of 1 cm. in such a way that the point of the needle was not more than 3 mm. below the surface of the cortex and did not enter the ventricle. The desired infecting agent was introduced into the brain through the needle. The needle was withdrawn in the following manner: After its depth had been reduced one-half, strong suction was made on it, and the needle was removed completely. This was done in order to clog the needle with a plug of supposedly sterile brain tissue. The wound was swabbed with iodine and closed without drainage.

Infected foreign substances were first employed as a means of stimulating the formation of an abscess by direct implantation. The various objects used were fragments of glass, short-sealed capillary tubes and small bits of marine sponge. Different strains of staphylococci and hemolytic streptococci obtained from human sources and from infections in cats were used. The objects so infected were placed

meticulously into the brain through a large bore needle in the manner just described. The nearest approach to an abscess was seen in two cats which had been treated with a marine sponge infected with Streptococcus haemolyticus. The animals died within thirty-six hours. There was a definite reactive process about the sponge, but no real abscess had formed. The other animals remained well; they were killed one or two months later, and gross examination of the brains did not show evidence of the formation of an abscess.

I then decided that if the bacteria were injected into an area of gliosis, a more active localized lesion might result. Eight cats were treated by a stab wound of the brain. In from ten to fourteen days, after a well developed glial reaction had taken place, a few minims of a culture of Staph. aureus or Str. haemolyticus were injected into the traumatized area. Several of the cats died of fulminating meningitis which in one case was the result of a ventricular injection. In the other animals there was no clinical reason to suspect the development of an abscess, and the necropsies gave negative results.

The extreme resistance of the brain to experimental infection suggested the idea that some culture medium on which bacteria grow should be used. Various mediums were tried. The first of these was a broth medium of cat's brain. The cultures were inoculated with either Staph. aureus or Str. haemolyticus and a heavy growth was obtained. The brain was taken out of the cultures and mashed, and 4 minims was injected into the cat's brain through a hypodermic needle. Although ten cats were so treated, in no instance was an abscess suspected clinically or seen at autopsy. In like manner, the clotted blood from each animal was infected and injected into its brain. Plain agar was used similarly. The animals failed to show any evidence of abscess of the brain throughout a period of six weeks.

If one assumed that the technic in these experiments was satisfactory, it seemed evident that the bacteria used would not produce abscesses. It was decided, therefore, to use different types of bacteria. The colon bacillus was selected because of the ease with which it is grown. Plain agar to which colon bacillus had been added was injected into the brains of several cats. The infection proved overwhelming. Not only did the brain show marked evidence of toxicity, but the infection was present throughout the body. The animals died within forty-eight hours. At necropsy, there was no definite localized reaction at the point at which the infecting agent had been introduced.

Pneumococcus or Diplococcus pneumoniae, type III, was then tried. Since the organism is cultivated best on blood agar, this medium was employed. Three cubic centimeters of blood agar was used; its temperature was maintained at 45 C. One cubic centimeter of broth medium made of cat's brain was added to blood agar slant on which a vigorous growth of pneumococci was present. After sufficient agitation and just before the time of injection, the suspension of concentrated broth was added to the melted blood agar. The infected blood agar was then drawn up into a tuberculin syringe, a sterile hypodermic needle was attached to the syringe, and 4 minims of the material was injected into the substance of the brain. As in the previous experiments, a two-stage operation was employed. Two cats were used. One died two days later of meningitis. A section of the brain revealed that the blood agar had broken into the ventricle. There was an area which suggested a beginning abscess. The other cat died seven days after the injection. The brain was removed, and on gross inspection the dura was adherent to the cortex directly beneath the cranial defect. There was no evidence of meningitis, and the convolutions on the side of and about the site of the injection were slightly wider than normal. Palpation of the infected side suggested fluctuation. Coronal sections of the brain disclosed an abscess, 6 mm. in diameter. It was well circumscribed, with beginning encapsulation. In the center of the abscess the blood agar which had been injected could be identified easily. A smear and culture of the pus showed that the infecting agent was the type III pneumococcus. The ventricles were displaced to the opposite side, and the medial portion of the abscess was in close relationship to the ventricle.

Clinically, the latter animal was interesting. It was apathetic for seven days following the injection, and means employed to make it walk met with a growl. It had definite slow-growing contralateral hemiplegia and a constant rotatory nystagmus. The animal died in a tonic convulsion with the entire body turned away from the lesion. The abscess was adjacent to the motor area.

Was the abscess the result of the organism or of the reaction of the brain to the blood agar? To answer this question, 4 minims of sterile blood agar was injected into a cat's brain. The animal remained well for three weeks and was then used in another experiment. Investigation of its brain at death, one month later, showed no reaction simulating an abscess. Part of the injected blood agar had been absorbed.

Fig. 1.—The first abscess produced. The upper section shows the blood agar in the anterior portion of the abscess cavity.

Since the production of the first experimental abscess of the brain, four additional cats have died with similar lesions. One cat lived for eight days. The clinical picture in this case was not so clearcut, although the cat became quite apathetic after the second day. There were slight contralateral hemiparesis and definite rotatory nystagmus. This animal's death was not observed, but there was no deformity of the body when it was found several hours later. The brain did not appear abnormal to gross inspection. The hemispheres were equal in size and shape. There was questionable widening of the convolutions on the side of the injection. When the brain was cut in coronal sections, an abscess, 4 mm. in diameter, was exposed. It was situated 3 mm. below the cortex, and its medial boundary was in close relationship to the ventricle. The ventricle on the same side was compressed, and the ventricular system was displaced to the side opposite the lesion. The abscess was circumscribed and had a fairly definite wall. It contained pus and the blood agar medium. The pus was loaded with pneumococci, which were proved to have the same characteristics as those injected.

The second animal in which an abscess developed, the third animal of the series, died within three days. From the time it regained consciousness after operation it became apathetic. Little could be gained from a superficial neurologic examination. Nystagmus did not develop, nor could one say that the animal showed hemiparesis. By the second day it was semistuporous, and during the next twenty-four hours it went into coma and died. At necropsy the brain appeared normal. There was no evidence of meningitis. The convolutions were not distorted. The dura was adherent to the cortex beneath the cranial defect. Section of the brain in the usual manner revealed an abscess in its early stages. It was located about 3 mm. beneath the cortex and compressed the ventricle only slightly. There was no shift of the ventricular system. The cavity abscess was small and contained about a minim of pus and the injected blood agar. The white matter in this area was edematous.

Of all the abscesses that I was able to produce, the fourth was of the longest duration. The cat in question, after a clinical course similar to that of the afore-

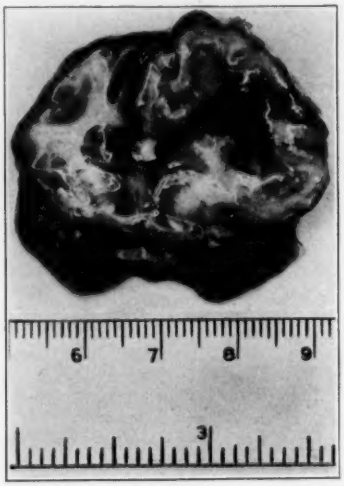

Fig. 2.—The cavity of the fourth abscess produced.

mentioned animals into which injections had been made, died on the tenth day. On inspection, the brain showed an increase in the size of the hemisphere into which the injection had been made. The convolutions were yellow and wider than normal. On section, the abscess was found to be 10 mm. in diameter, the largest of the series. It contained pus and the injected blood agar. The medial border of the lesion was in close relationship to the ventricle, which it compressed. The ventricular system was displaced to the opposite side.

The fifth abscess was caused by the Str. pyogenes. The animal in question died on the fifth day. There was nothing unusual about the clinical course. Grossly, the brain was normal except for less resistance to palpation at the site of the injection. Section of the brain disclosed a small abscess which contained thick greenish pus and the injected blood agar. The lesion was well localized and had a well defined wall. The ventricular system was only slightly displaced to the opposite side.

Histologic examination of the abscesses showed the localized inflammatory reaction. In the first and fifth animals, the abscesses showed beginning formation of a capsule. However, the sections have not been studied sufficiently to give a detailed report.

In the later experiments two difficulties arose. One has to do with the virulence of the pneumococcus. This organism loses its toxicity rapidly when subcultured. It is therefore occasionally necessary to pass the bacteria through a mouse in order to increase the virulence. The second difficulty has been in the injection of the infected blood agar. If the infected blood agar is injected after it has hardened in the syringe, there is little danger of its seeping back along the sides of the needle. The use of this technic has prevented meningitis and superficial infection of the wounds.

Summary.—The experimental method described represents a successful means by which abscesses can be produced in the brains of cats. The technic consists of a two-stage operation, the first step consisting of a small cranial defect and the establishment of adhesions between the dura and the cortex. At the second operation, a blood agar culture of pneumococci, type III, or Str. pyogenes was injected into the brain substance through the exposed dura. The five lesions produced have conformed to the gross pathologic descriptions of abscesses of the brain. The longest duration of a lesion has been eight days following infection, and the shortest, three days. The specimens have not been studied sufficiently to warrant any pathologic description.

(The expense for this work was defrayed by a donation from the Francis Clark Fund for Neurosurgery.)

DISCUSSION

DR. F. C. GRANT: The steps that Dr. Groff has made in his approach to the production of artificial abscess of the brain are important. So far as I know, it has not been possible to produce abscess of the brain artificially in animals without the death of the animal occurring within five or six days from the introduction of the infected material. Dr. Groff has been able to keep his animals alive for ten days, and in one instance not reported in this series, for more than a month. This has been accomplished by selection of the infected material and proper attenuation of the organisms used.

The purpose of this work was to produce abscess of the brain so that studies could be made of the pathologic changes, the formation, the clinical course and the proper method of treatment. Hitherto, the study of abscess of the brain has been based almost wholly on its occurrence in man. If the abscesses can be produced in animals, a wide field for investigation will be opened up not only as to the pathology but also as to the most suitable time for operation. It will make possible a trial of various methods of drainage and other forms of treatment which may have direct bearing on the treatment of abscess of the brain in man.

DR. CHARLES H. FRAZIER: Surgical treatment of abscess of the brain is in a transitional stage. Before 1918, perhaps the majority of abscesses of the brain were treated by the otolaryngologist, who happened to be in charge of the condition (mastoiditis, a discharge from the ear or a sinus infection) when the abscess developed. The otolaryngologist operated only occasionally, and he was not familiar with the problems of surgical intervention in the brain. Since 1918, the problem has attracted the attention of the brain surgeon. Prior to that, the mortality was distressingly high. Since then, the mortality has gradually been reduced. Before 1918, once the diagnosis was made, the operation was not deferred. Now the important question in the mind of the neurosurgeon is not how soon he may operate, but how long he may wait. The thoughts of the neurosurgeon are concentrated on the pathologic changes and the process of encapsulation. To attempt to drain in the stage of encephalitis, before encapsulation has occurred is, of course, futile. No operation for abscess of the brain should be undertaken before encapsulation is an accomplished fact. More than that, encapsulation must have been accomplished by connective tissue elements and not by the neuroglia. It is only the former which supply the necessary protection. Unfortunately, the process of encapsulation does not proceed at a uniform rate. The completion of the process is attained more rapidly in some cases than in others, and in some cases fibrous encapsulation may not occur within the period of safety, that is, before the signs

of pressure may be so great that operation seems imperative. We still have a great deal to learn, and I hope that with Dr. Groff's ability to establish an abscess in the experimental animal we may learn much about the process of encapsulation that will be of incalculable value in the determination of the most favorable time for surgical intervention.

VERIFIED TUMOR OF THE TEMPORAL LOBE: A CRITICAL REVIEW OF FIFTY-TWO CASES. DR. STUART N. ROWE.

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OBSERVATIONS ON CEREBROSPINAL FLUID PRESSURES. DR. RUBIN M. LEWIS and DR. WILLIAM DUANE.

Cerebrospinal fluid pressures at the cisterna magna, with the animal in the horizontal position, have been reported by several investigators. The pressures vary from 50 to 200 mm. of water. The observations were made with manometers of 1 mm. bore. Changes in the capillarity and the volume have been discussed by Leonard Hill, Becht and others as being important factors which affect the accuracy of observations of pressures in the subarachnoid space. We have demonstrated the effect on the pressure values of the removal of small amounts of fluid from the subarachnoid space.

A laboratory table was described for use in experiments in tilting; the animal can be rotated on it about an axis passing through the point of the needle at any arbitrary point. A closed method for measuring pressures was presented. The method provides for corrections of factors concerning capillarity; it overcomes changes in volume, and possesses an extremely low factor of inertia. The apparatus also affords means of photographic recording of changes in pressure.

Dogs were used in all of the experiments. Sodium isoamylethylbarbiturate was used intraperitoneally as the anesthetic. Pressure studies were made with open manometers of 1 mm. bore and also with the closed manometer. Lantern slides of the changes in pressure in relation to posture were shown, with diagrams of the manometer which was presented. Photographs of subarachnoid pressures were also demonstrated. The apparent discrepancies in the reported pressures in the subarachnoid space were explained by observations of pressures with the animals in the prone, supine and side positions, with the spinal canal in the horizontal plane. The rotation about the longitudinal axis and the observed pressures are presented as a new contribution to the knowledge of the physiology of the spinal fluid system.

DISCUSSION

DR. CHARLES H. FRAZIER: Are the observations of Dr. Lewis in agreement with Weed's work?

DR. RUBIN M. LEWIS: With the open manometer of 1 mm. bore, our results are the same as those reported by Weed for his postures. However, we have gone one step further in our observations and have reported pressure values for the prone and the supine positions with the animal's spinal canal in the horizontal plane. Our values are different when observations are made with the closed system manometer. This difference is caused by the corrections for capillarity and the prevention of changes in pressure by the maintenance of a constant volume.

We performed the experiments in which the animal was rotated about his spinal canal with both live and dead animals. The pressure values were similar in the two cases. The experiments were performed in an attempt to understand the mechanism of the changes in pressure. Because of the similarity of the pressures, we felt that vascular reflexes played a relatively unimportant part.

STATISTICAL STUDY OF THIRTY-NINE FIBROBLASTOMAS OF THE SPINAL CORD. DR. CHARLES H. FRAZIER.

This article will be published in full elsewhere.

TUMORS OF THE SPHENOID RIDGE. DR. B. J. ALPERS.

This article will be published in full elsewhere.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Joint Meeting, May 2, 1933

BYRON STOOKEY, M.D., *President, in the Chair*

SPASTIC HEMIPLEGIA IN AN INFANT PRODUCED BY A CONGENITAL CYST ENTIRELY REPLACING THE CEREBELLAR VERMIS. DR. JOHN E. SCARFF (by invitation).

The patient, aged 16 months, had been admitted to the hospital with a right spastic hemiplegia and choked disk. Ventriculography revealed an extreme degree of symmetrical hydrocephalus of the lateral and third ventricles. Suboccipital exploration disclosed a large, thin-walled cyst, which apparently completely replaced the cerebellar vermis. The cyst was evacuated and the wall entirely removed. An uneventful recovery followed. Since then, the child has begun to walk, apparently in normal fashion.

The case was presented to show the hemiplegia produced by a cerebellar lesion and the effect on the gait due to the absence of the vermis.

DISCUSSION

DR. H. A. RILEY: I should be chary in describing this child as one without a cerebellar vermis. I think that one can never be certain of the exact anatomic situation until the specimen is available for examination. From what I saw of the pictures, it seems possible that a cyst is growing from the lower portion of the cerebellum, extending upward and pushing the whole vermis up underneath the tentorium, dislocating the cerebellum forward and pushing the midline structures out of sight, the cerebellar vermis being dislocated out of its normal position. Dr. Scarff had a better view of the situation, but from what I can see of the illustration I do not think that one is justified in stating that there is no vermis.

DR. JOHN E. SCARFF: I acknowledge the propriety of Dr. Riley's remark.

DR. H. G. WOLFF: May I ask whether there were actual defects in the "point-to-point" test and in the "stopping and starting" tests? I saw the disability in walking, but that could be explained by the child's lack of familiarity with walking.

DR. JOHN E. SCARFF: The child is just learning to walk. It is rather early to state the results of the tests mentioned. I think that under the circumstances the patient does remarkably well.

GASSERIAN GANGLION SYNDROME PRODUCED BY A TUMOR OF UNUSUAL NATURE. DR. JOHN E. SCARFF (by invitation).

An Italian man, aged 40, a tailor, had pain in the right side of the face, not typical of trigeminal neuralgia, hypesthesia of the right side of the face, hypalgesia of the cornea, weakness and atrophy of the muscles of mastication on the right side and, more recently, progressive paralysis of the extra-ocular muscles, together

with Horner's syndrome. A preoperative diagnosis was made of tumor originating from the region of the gasserian ganglion. A preliminary operation was performed, with division of the sensory root of the trigeminal nerve at its junction with the pons, the suboccipital approach advocated by Dandy being used. Two weeks later exploration of the middle fossa on the right side revealed in the apex of the middle fossa a highly vascular tumor, chiefly extradural, and apparently invading the bone of the base. Partial removal was accomplished. The patient had an uneventful postoperative course. Some months later death occurred following a prolonged status epilepticus of sudden onset.

Autopsy revealed a large tumor, essentially extradural, invading the bones of the base of the skull, the sphenoid sinus, the posterior wall of the right orbital fossa, the floor of the middle fossa and the basilar part of the sphenoid, and entirely filling the cavernous sinus. On microscopic examination, this tumor was found closely to resemble salivary gland tissue.

DISCUSSION

DR. H. A. RILEY: Has Dr. Scarff consulted an embryologist or an anatomist as to the possible way by which an embryonic inclusion or "rest" could have taken place? As I remember the embryology of the salivary structures, they form as buds from the buccal cavity. Perhaps Dr. Deery might give some information as to whether there is any possibility of the inclusion of an embryonic rest in the region of the gasserian ganglion through placode formation. I do not know whether Dr. Deery has investigated the trigeminal nerve placode formation; I am interested in knowing whether the origin of the tumor could be traced back to the inclusion of potential salivary cells from the buccal mucous membrane in connection with placode formation which might have given rise to such a neoplasm.

DR. EDWIN M. DEERY: From the close relationships, I think that such inclusion is highly possible. I do not know definitely of any case so reported.

DR. JOHN E. SCARFF: I made inquiries and gathered the impression that the buccal mucous membrane and the lining of the sinuses and of the lacrimal and the salivary glands are closely related to each other embryonically. It is not uncommon, I learned, to find lacrimal gland inclusions occurring as tumors within the orbit, the nasal septum, the hard and soft palate and the accessory nasal sinuses. Dr. Ewing believes that this tissue is also closely related to that which enters into the formation of Rathke's pouch, and to the anterior lobe of the hypophysis.

SPINAL METASTASIS FROM A CLINICALLY BENIGN THYROID. DR. JOHN E. SCARFF (by invitation).

A man, aged 27, was admitted to the service of Dr. Foster Kennedy at Bellevue Hospital in September, 1932; a diagnosis of tumor of the thoracic cord was made. A laminectomy performed by Dr. Byron Stookey revealed a diffuse tumor involving the spines and bony laminae of the third and fourth dorsal vertebrae. A microscopic study of this tumor revealed normal-looking thyroid tissue of the colloid type. According to all clinical standards, the thyroid gland was of normal size and character. Repeated roentgen treatments have been given since the operation and have brought about marked improvement.

DISCUSSION

DR. GEORGE H. HYSLOP: As I have seen the patient before the operation and afterward, I think that the question may be raised as to whether or not this neoplasm was an embryonic rest. About six years ago I saw a patient with a compression lesion in the upper part of the thoracic cord, who was operated on at New York Post-Graduate Medical School and Hospital after a preoperative diagnosis of extramedullary or extradural tumor. On histologic study the tumor was found to be malignant thyroid tissue compressing the spinal cord. After it was found, reexamination of the thyroid gland itself was made, and a small nodule

was discovered. The thyroid gland was extirpated, and the nodule was reported to be "malignant." The patient subsequently came under my observation at the Memorial Hospital with a transverse lesion of the cord and with motor and sensory disability. Following heavy doses of roentgen rays the patient recovered the ability to walk.

DR. BYRON STOOKEY: I performed the operation referred to by Dr. Hyslop. Dr. Scarff and I have been interested in cases of metastases from the thyroid to the vertebrae and bones in general, and I think that Dr. Scarff knows about that particular patient. If I am not mistaken, she was first operated on for a tumor of the thyroid gland, and afterward she had a laminectomy.

DR. JOHN E. SCARFF: The patient described by Dr. Hyslop had a goiter, clinically diagnosed as benign, removed at New York Post-Graduate Medical School and Hospital by Dr. Charles Gordon Heyd. Grossly and microscopically, the growth proved to be a simple adenoma. About two weeks later Dr. Byron Stookey removed from the spinal canal of the same patient a tumor, which also had the microscopic appearance of a benign adenoma of the thyroid. This case was reported in detail by Dr. Locke MacKenzie in the *American Journal of Surgery* (**6**:372, 1929). We saw this patient in the follow-up clinic last spring. She had had a massive recurrence of the tumor of the spine, but there was no evidence of a local recurrence of the original tumor of the thyroid gland.

DR. GEORGE H. HYSLOP: Is it your opinion that in both of these cases the tumors in the spinal cord arose from aberrant rests, or do you think that they were of metastatic origin?

DR. JOHN E. SCARFF: That question is not settled. There are two schools of thought, neither of which can definitely prove its theory. One thinks that the tumors in the spinal cord are due to aberrant rests, and the other believes that they are of metastatic origin. Our theory regarding malignant tumors may have to be somewhat revised. In 1870, Cohnheim reported the first of these cases of metastasis from apparently benign thyroid gland tissue, but he also reported that "normal" thyroid gland tissue had invaded the inferior thyroid vein at one point. One of the criteria of malignancy now accepted is specifically this invasion of the blood vessels by glandular tissue. Some definitely believe that all cases of so-called metastases from an apparently normal thyroid gland, if carefully studied in serial section, would reveal some point where thyroid tissue had migrated into blood vessels. Approximately seventy or eighty cases of metastases from clinically benign thyroid glands have been reported. I believe that in only about thirteen or fourteen of these has the thyroid gland itself been studied serially, but in all of the cases in which it has been so sectioned invasion of the blood vessels by glandular tissue has been found.

About 30 per cent of the metastases in the bone are to the skull, and about 25 per cent to the spine. There is apparently no relationship between the type of the thyroid gland itself and the type of metastases produced.

DR. LEWIS D. STEVENSON: Until Ewing published his book, the thyroid gland had not been given careful microscopic study in any of these cases; he doubts whether if the glands were carefully examined, one would not, as has just been suggested, find a carcinoma of the thyroid. Another thing pointed out by Ewing is that colloid goiters may form metastases in the bones, skull or spine, which look benign but in reality are originally malignant or carcinomatous. There is a tendency for the metastases to assume benign appearances when in reality they are malignant.

PSYCHIC EPILEPTIC EQUIVALENTS IN ASSOCIATION WITH TUMOR OF THE BRAIN. DR. LEO M. DAVIDOFF.

In cases of epilepsy in which the convulsive element is slight or absent, psychic disturbances of longer or shorter duration may constitute the entire picture. These disturbances may consist of absences of consciousness almost too brief to be noticed; there may be a slight slowing of the pace in walking, hesitancy for half a sentence

in speaking or a moment of apparent loss in thought. If the period of disturbed consciousness is increased, automatic movements, or compulsions, occur, and these may take on a complicated form. The patient may undress himself, walk naked into the street, become unusually belligerent or even commit a crime, such as theft, arson or assault.

One feature common to all these epileptic equivalents is the amnesia which follows the act. These and other psychic manifestations are fairly common in patients with epilepsy due to toxic, metabolic or unknown causes, but their occurrence in patients with organic disease of the brain, such as tumor, is sufficiently rare to warrant the report of two cases.

CASE 1.—L. B., a man, aged 52, an employee of the city, was admitted to Beth Israel Hospital on Feb. 13, 1932, with an illness that began early in 1930 with a sudden attack of unconsciousness. This recurred about six times during two years. In addition, he had lapses of memory; for instance, if told to sweep the stairs he might take the broom, walk down the stairs and come up again, thinking that he had done the job. For seven months before admission to the hospital, vision had failed gradually, so that finally he could distinguish only the difference between light and darkness. In addition, the wife reported certain "queer spells." For example: Once she returned home and found him lying on a couch singing in an "unnatural" voice the first line of the song "Sweet Adeline." She spoke to him, and even shook him, but nothing she did would make him stop. This lasted for about five or ten minutes, and then ceased spontaneously. He appeared dazed and remembered nothing of the incident. On another occasion he went to the bathroom, and when he failed to come out within a reasonable time his wife went in and found him sitting on the toilet, staring ahead, twiddling his thumbs and repeating "ninety-nine times ten" over and over again. Once more she was unable to interrupt this strange behavior; it ended spontaneously, and again he did not remember anything about it.

Neurologic examination revealed bilateral anosmia and bilateral optic atrophy, with swelling of the disks. Studies after injections of air confirmed the clinical impression of the presence of a bilateral subfrontal tumor.

An operation was performed on March 7, 1932. A large meningioma of the olfactory groove, chiefly on the right, but extending under the falx and involving also the left side, was removed. The patient recovered visual power and has had no spells of any sort during the fourteen months since the operation.

CASE 2.—C. C., a schoolgirl, aged 9, of Catholic Italian parentage, was a pupil of a parochial school and was frequently taken to church services and to other religious functions. In addition, she often heard prayers at home by her very devout mother. Except for attacks of measles and chickenpox, she was perfectly well until the age of 4½ years, when she was said to have fallen. The fall was of relatively small importance, but thereafter she began to have strange spells which had slowly increased in frequency and duration.

The spells consisted of the following: Whatever she might be doing or saying was interrupted. She made a deprecatory gesture with the right hand and declared, "Pooh, pooh, to the devil." She then threw a kiss while announcing, "To God." These spells had been absolutely stereotyped. The patient did not remember any of the details. She frequently seemed listless and tired following a spell; she might prefer to stay away from school for the rest of the day; sometimes she slept afterward. In the period between spells, she seemed perfectly well, mingled and played well with other children and did her school work satisfactorily. She complained of no headaches, paralyses, twitchings or sensory or equilibratory disturbances.

The neurologic status was entirely normal. Roentgenograms of the skull showed a calcified mass in the right cerebral hemisphere, approximately 10 cm. in diameter. The nature of the calcification suggested that seen in an oligodendroglioma. This diagnosis had not yet been confirmed by operation.

DISCUSSION

DR. BYRON STOOKEY: Dr. Davidoff has said correctly that there is nothing to be seen in case 1. I do not know whether he referred to the scar, but if he did not, I do. One cannot tell that this patient has been operated on, and yet a large transfrontal flap was turned down.

DR. JOSHUA H. LEINER: Was there a history of trauma in this case?

DR. LEO M. DAVIDOFF: No history of trauma was obtained.

HEMANGIOMA OF THE CEREBELLUM. DR. IRA COHEN.

A girl first came under observation in 1926, at the age of 4 years. She was admitted to the neurologic service of Mount Sinai Hospital because of headache, vomiting and squint, of seven weeks' duration, and because of staggering gait lasting one day. The headache with which the illness began lasted four days; it was followed by a free interval of five weeks; then it returned with increased severity. The vomiting was associated with the headache.

There was evidence of internal hydrocephalus, with dilated veins of the scalp. There were choking of the disks up to 3 diopters, weakness of the left external rectus muscle, generalized hypotonia, ataxia on the right and some degree of adiadokokinesis. The deep reflexes in the upper extremity were lively; those in the lower, depressed. The abdominal reflexes were present; there was no Babinski sign.

A diagnosis of cerebellar tumor was made, and a suboccipital exploration was performed on February 19. The operator believed that he felt some resistance to the brain needle in the left cerebellar lobe. Further exploration was deferred.

Roentgen therapy was instituted. During the next two months the papilledema receded. The patient was discharged from the hospital three months after the operation.

During the next five years she was seen at the follow-up clinic. Her condition remained stationary. The only abnormal sign was a slight fulness of the retinal veins.

In January, 1931, following a slight trauma, she had occasional vomiting. In April, fulness of the operative site and early papilledema appeared. She was referred to the hospital, but it was June before she entered. The operative site was bulging, and there was nystagmus on extreme lateral gaze. Choking of the disks was from 2.5 to 3 diopters.

On June 8, the old midline incision was reopened. A cystic protrusion of the vermis, covered by a very thin layer of brain tissue, was seen. The cerebellar lobes were pushed far apart by the cyst, which contained about 40 cc. of yellow fluid and seemed to occupy the entire vermis. When it was opened the floor was found to be tumor tissue; gelatinous material partly filled its upper part. The tumor was excised with the cautery loop. Unroofing of the fourth ventricle except for a narrow rim left at the extreme lower end was required in order to remove all tumor tissue. The dilated iter could be seen above. The pathologic report was hemangioma of the Lindau type.

During the first two postoperative weeks there were profound ataxia and weakness, and the child did not talk. Improvement was then rapid. The patient left the hospital twenty-one days after the operation.

The only residua observed at the time of presentation were a tendency to posturing of the head and a slight adiadokokinesis.

Hemangioma is neither rare nor very common. The slowness of its growth is shown by the five year interval between the palliative and the radical procedures. The patient showed remarkably few signs considering the extent of vermis removed. Although the pathologic picture was that of a Lindau type of hemangioma, there was no hemangioma to be seen in the retina or elsewhere.

DISCUSSION

DR. JOSEPH H. GLOBUS: I wish to take exception to the use of one word. There is no "Lindau" type of tumor. There is a hemangioma described by Lindau which is associated with retinal anomalies, and this tumor belongs to that group, although no retinal anomalies were found.

DR. LEO M. DAVIDOFF: I wish to add a word in agreement with Dr. Globus on that point. I think that it is wrong to call this a "Lindau tumor," just as it would be wrong to call an acoustic neurofibroma Recklinghausen's disease. I once reported a case of exactly this type with no other angioma in the body, and I was criticized accordingly.

DR. IRA COHEN: I think that the exceptions of Dr. Globus and Dr. Davidoff are justified. However, there have been cases in the literature in which angioma of the retina has been sought and found only at a later time. In closing, I wish to mention two interesting features which this case presented; one is the rather slow growth of the tumor, as shown by the five year interval between the palliative and the radical operation, and the other is that, even though I cannot say that the entire vermis is gone, the child has lost a large part of the vermis and seems to get along fairly well without it.

DR. JOSEPH H. GLOBUS: "Lindau" is a name which should be associated with this type of tumor, for the reason that he first drew attention to the existence of hemangioma in the cerebellum. Many cases of this type had been reported prior to Lindau's description. Unquestionably Lindau deserves credit in making it possible for one to identify these growths. In dealing with this type of neoplasm I have made it a rule to put the name of Lindau in parenthesis, not merely to credit him with the discovery but to stimulate the neurologist or surgeon to look for other anomalies which may exist in association with this type of tumor.

MENINGIOMA PRESENTING TRIGEMINAL SIGNS. DR. IRA COHEN.

Five and a half years before presentation a woman was admitted to the neurologic service of Mount Sinai Hospital. At that time she had been ill for four months. The first symptom was temporary amaurosis, which came on in attacks, five or more a day, each lasting from three to five minutes and being associated with mild headaches. After three weeks of suffering she entered a hospital; the nasal sinuses were operated on. Vision decreased, and when she left the hospital she was almost blind in the right eye and was rapidly losing vision in the left. Four days before being admitted to Mount Sinai Hospital, a sudden severe "hammering" headache developed, which lasted for twenty-four hours.

On examination, she had light perception in the right eye; the pupil was dilated and fixed; the disk was gray, and there was 2.5 diopters of swelling on that side and 3 diopters in the other eye. There was no change in the field of the left eye. The only other sign was a slightly more active ankle jerk on the left.

Encephalography was unsatisfactory, but the roentgenogram showed clouding of both antrums and ethmoids, so she was again subjected to nasal operations and washings.

After she had been under observation for six weeks there developed numbness of the right side of the face and the jaw deviated to the right. The numbness preceded pain by four days. Six days after its onset there was complete loss of sensation in the right side of the face.

A diagnosis of a tumor pressing on the right gasserian ganglion was made, and the patient was operated on. A flap was turned down on the right side, and a soft endothelioma, about the size of a small peach, was removed from the region underneath the temporal lobe. Its mesial margin was against the clinoids. It was adherent to the dura of the floor of the skull; small bits of tissue had to be left.

Three days later, sensation began to return to the face. At the time of presentation the right eye saw moving objects. The patient had no other abnormal neurologic signs.

The interest in the patient rested partly on the facts presented in connection with the next case. One should again emphasize that a case should not be allowed to progress to blindness while one fixes attention on the nasal sinuses. The late but rapid onset of the trigeminal signs is worthy of attention; these signs helped to establish the diagnosis and localization. The patient presented no signs of any recurrence after five and a half years.

PRIMARY TUMOR OF THE GASSERIAN GANGLION. DR. IRA COHEN.

A married woman, aged 31, was admitted to the neurologic service of Mount Sinai Hospital in January, 1932. Six years prior to admission she had experienced a sudden sharp pain over the inner canthus of the left eye. The pain was of needle-like character and of short duration. It was repeated and at times was associated with twitching of the upper eyelid. Following the prescription of glasses, she was relieved for four and one-half years, though at times there was a mild twinge. About one and a half years prior to her admission to the hospital the pain returned. It assumed the character of electric shocks and was felt in the eyeball. Later it spread so as to involve the entire left side of the face. It came on as often as a hundred times a day, only occasionally awakening her at night. Chewing, grimacing or washing the face did not provoke the pain. For a year she noted an increasing prominence of the left eye and some drooping of the upper lid on that side, associated with difficulty in opening the eyelids wide. For five months there was dryness of the nose. Roentgen examination of the skull showed a partial destruction of the bones of the left sphenoid fissure. The report read in part: Roentgen examination shows a destructive process involving the left temporosphenoidal fissure; the fissure on the left side is approximately twice the width of the right. The patient presented left exophthalmos. The left pupil was larger than the right and reacted very sluggishly to light, while the right responded promptly. There were ptosis of the left eyelid and restriction of movement of the left eyeball in all directions, especially in upward and downward gaze. The ophthalmologist reported paresis of all branches of the third nerve, but no involvement of the fourth or sixth nerves. The fundi were normal. Slight hyperalgesia over the skin innervated by the first branch of the left fifth nerve was present. Sensation in the other branches and motor power were intact. There were a right central facial weakness and an increase in the deep reflexes on the right. Other laboratory data threw no additional light on the case. A preoperative diagnosis of a tumor, probably a meningioma of the sphenoid ridge, was made.

Through an osteoplastic flap on the left side, made under local anesthesia, the middle fossa was explored. The tumor was extradural, mesial and anterior to the foramen spinosum. It formed an elevation of about 2 cm. in the floor of the fossa. The condition of the patient necessitated a second stage operation, which was not performed until eighteen days later because of a temporary aphasia which appeared after the first operation. The flap was turned down, and the tumor was exposed again intradurally. The dura overlying it was incised, and a well encapsulated growth, measuring about 4 by 3 by 2 cm., was removed. The tumor was removed first and then its capsule. The bed left after the removal lay back of the sphenoid fissure. The internal carotid artery could be felt in its mesial posterior part. The bulk of the tumor was anterior to the ganglion along the course of the first branch. Whether it sprang from the first branch or from its junction with the ganglion could not be determined. The tumor was reported as a neurinoma.

At the time of presentation the patient was free from pain; she had paresis of the third nerve and hypalgesia of the area of the fifth nerve.

The case was of interest because primary benign tumors arising in this location are rare. If one accepts Altman's classification, there are but twenty-six other primary tumors in the literature. Dr. Cohen believes that its site of origin was about at the junction of the first root with the ganglion, from which point it extended forward. The approach was unorthodox. From the exposure of the first stage it was thought wise to approach the tumor in the same way in the second stage.

DISCUSSION

DR. ISRAEL STRAUSS: The first case interests me because I do not suppose that today the condition would be diagnosed and treated as sinusitis so long before it would be recognized that the symptoms were due to an intracranial lesion. Yet it not infrequently happens that persons with disturbance of vision are sent to rhinologists, and rhinologists unfortunately often find disease in the nose. Most people have slight variations in the anatomic configuration of the nose; many cases show slight changes in the roentgenogram which are not indicative of disease. I have often wondered why it is that rhinologists and internists frequently find so much abnormality in the nose. There is an explanation for some of this activity which I do not wish to express now; but when a person has ethmoiditis or suppurative sphenoiditis with involvement of vision, the examination of the fundus generally will show a high grade unilateral papilledema, and occasionally even bilateral papilledema. It is interesting to note that the disturbance in vision is in the nature of a central scotoma. It is generally unilateral. Neurologists know that a very high grade of choked disk may continue for a long time without any disturbance of vision. If one finds unilateral papilledema with a well marked loss of central vision, one can expect a pathologic condition in a sinus or elsewhere. I think that as time goes on these points will become more generally known; a human being need not lose vision through optic atrophy before the real seat of the trouble has been discovered and removed.

DR. SAMUEL BROCK: Did not the first patient have a suprasellar meningioma which extended laterally, giving trigeminal signs?

DR. IRA COHEN: No; the tumor extended laterally from the clinoids and was found under the temporal lobe.

DR. BYRON STOOKEY: Are neurinomas common in that position?

D. J. H. GLOBUS: No, they are not common.

DR. IRA COHEN: In answer to Dr. Stookey's question as to the relative rarity of this type of tumor, if one accepts Altman's classification of primary tumors, only about twenty-six neurinomas and neurocytomas have been reported. He pointed out one thing I should like to speak of in connection with this patient. The primary neurinomas seem to spring from the junction of the root with the ganglion, and that is where I should localize this tumor, its situation being the junction of the first root with the ganglion. It would be difficult to say whether it sprang from the root or the ganglion but, affecting as it did the third nerve, a part of it must have been along the first branch; the bed extended far enough back to make me believe that part of the ganglion was involved in the process.

HISTOLOGIC FEATURES OF GLIOBLASTOMA MULTIFORME. DR. EDWIN M. DEERY.

Glioblastoma multiforme, the largest single type among the gliomas, appears to merit histologic subdivision. Within this tumor are differences, chiefly of the predominant maturation level, which provide a basis for subdivision. Cases of glioblastoma multiforme are not all equally malignant clinically, and it seems likely that the clinical variations which occur must have their basis in the variable histologic characters of the tumors.

An attempt has been made to divide cases of glioblastoma multiforme into groups on the basis of the histologic evidence of their malignancy. In order clearly to establish the histologic subgroupings, the basic neoplastic elements composing the tumors are reviewed. These elements form a graded series of maturation stages from the primitive neuro-ectodermal cell to the astrocyte, which series is roughly parallel to but not identical with the stages found in normal histogenesis.

On the basis of the predominant basic cell type found in each case, three groupings are suggested. The least differentiated, most malignant group is characterized by the predominance of primitive neuro-ectodermal cells and spongioblasts, the latter with numerous mitoses. The intermediate group is composed of tumors in which older polar spongioblasts that have for the most part achieved fibril formation predominate. In the most differentiated and least malignant group are the tumors containing a predominance of astrocytic elements.

When the duration of neurologic symptoms to the date of surgical intervention was studied in these three groups, there was found a direct relationship between the histologic evidence of malignancy and the clinical course.

It is urged that an attempt be made, when making the diagnosis of glioblastoma multiforme, to incorporate in the diagnosis an expression of its histologic malignancy which will provide a more exact criterion than is available at present for correlation with the clinical aspects.

DISCUSSION

DR. JOSEPH H. GLOBUS: I am somewhat hesitant in saying anything critical concerning the paper presented by Dr. Deery. I dislike to discourage by destructive criticism any work, particularly that presented by some one who most likely is making his first step in the field of neuropathology. However, I think that I should draw attention to a few points which, in my opinion, are not in keeping with fully established facts. Dr. Deery speaks of giant cells in spongioblastoma multiforme as something that is not characteristic of such tumors. They are cells which, in his opinion, are foreign to the tumors; they may, he says, be regarded almost as foreign body giant cells. This is at variance with my opinion, which is that giant cells are strikingly typical of spongioblastoma multiforme. Cushing and his co-workers have been able to reproduce tumor elements grown in cultures in which the giant cells have been reproduced, assuming the form and type seen in the original tumor. He and one co-worker have concluded that there is no question but that the giant cells are typical components of the tumor which at that time was still known and accepted by them as spongioblastoma multiforme.

The question as to the name of this type of tumor has been discussed several times. What are the advantages of introducing a new term which has no histologic basis? The old term has been in existence for years. The spongioblast is known to every histologist, embryologist and pathologist. The glioblast is known to a few men who have coined that term without good reason. Spongioblast designates an undifferentiated cell in the nervous system, which is the forerunner of the glia cell. It is still taught that a spongioblast is a primitive glia cell and that the glia cell is derived from the spongioblast. The term spongioblastoma is applied to a malignant form of glioma, indicating that such a tumor consists of undifferentiated glia cells or malignant glia cells. The glioblast, on the other hand, does not exist. I wish to ask Dr. Deery what he considers a glioblast to be. If there is no glioblast, what is a glioblastoma? Blastoma means true tumor. The addition of another word, such as "glia," means a tumor made up of glia cells; fibroblastoma means a tumor made up of fibrous tissue. A fibroblastoma is a benign tumor, and hence a glioblastoma is a benign tumor. Borst defined the term "blastome" as a true tumor (Aschoff, L.: Pathologische Anatomie, Jena, Gustav Fischer, 1923, vol. 1, p. 653). Any tumor which consists of benign cells is, of course, a benign tumor. The term blastoma does not imply malignancy. It merely defines the growth as a true new growth. The term glioblastoma merely gives a new name to the benign glioma; there is only one way to designate a malignant glioma: to call it a spongliоblastoma.

As to the further classification of the spongioblastomas, there are two reasons for such a procedure. Whenever one attempts to classify a tumor group, it is an attempt either to serve some practical purpose or to make an academic contribution. For practical purposes it is better to reduce the number of names given to these tumors. There are only two definite varieties of gliogenous tumors, with many transitional forms between them. My mode of classifying gliogenous tumors is to place first the spongioblastoma multiforme, which is a malignant tumor, and last the benign gliomas, and to name those in between as transition forms. Even the benign gliomas frequently became malignant. Every tumor must have a germinal center if it continues to grow. If such is the case, every tumor has a potentiality for malignancy. Even the benign glioma, the astrocytoma or oligodendroglioma, has germinal centers which are capable of progressive growth with the formation of typical spongioblastoma. I have reported such cases, and

recently I have been able to study fully autopsied material in which large masses of tumor tissue have been removed; the original benign character, as well as the malignant transformation, could be established. From the practical point of view, every gliogenous tumor is either malignant or potentially malignant. Cases of benign glioma that remained benign or dormant for many years are not numerous.

Academically, speculation is permissible and one can classify and name tumors more exactly. But can this be done to advantage? I defy any one to point out a tumor, even in the spongioblastoma group, and define it in terms of the predominant cell type, and say "this is this" and "that is that," and maintain that it will remain so for the rest of its biologic life. I have come to recognize limitations in one's ability to solve certain problems, and I have learned that not only can one be uncertain as to what a tumor is today, but one will be still less certain what the same tumor will be in a week or in a month from now. As there is no available method of examining thousands or millions of cells in the same tumor and of being assured that a cell in one place fully corresponds to a cell in another, one must be careful in making deductions. For the time being I think that it is wiser to consider the spongioblastoma multiforme as a malignant form of glioma and to retain that name, but not to attempt to subclassify the group in the belief that it may serve practical purposes.

As regards the correlation of the time factor with the histologic character of the tumor, attempts have been made frequently to synchronize the growth history of a tumor with the evolution of the clinical picture, and to determine on histologic grounds the span of life found in one type of tumor and not in another type. Dr. Deery tried to obtain an estimate from the clinical history, which in most instances has a rather vague beginning, and from the length of time the patient lived after the operation. It must be realized that the operative procedure in itself introduces uncertain elements, as it is so much dependent on the skill with which it is carried out, the location of the tumor and on many other factors which are as important as the type of cell found in the tumor. So that to predict seventeen months for one tumor and twenty-seven months for another is dangerous. For academic purposes such information could be gathered until proved or disproved.

DR. ISRAEL STRAUSS: This is an old battleground. I did not know until tonight why the term "glioblastoma" has had such an appeal. Dr. Deery informs us that it is in the National Nomenclature, and I have been an ardent advocate of the National Nomenclature.

Dr. Deery mentioned Dr. Penfield. In that article of Penfield are these statements: "The name spongioblastoma multiforme is descriptive, whether one believes that the true type cell is the apolar spongioblast or not. The name, polymorphous glioma, suggested by Roussy, Lhermitte and Cornil, is also descriptive. It seems best, however, to adhere to the name that was given to this tumor by Globus and Strauss who first clearly described in detail the neoplasm as an entity.

"The substitution made recently by Cushing and Bailey of glioblastoma multiforme has little in its favor. It does not clarify the conception of the tumor. No such cell as a glioblast has ever been described in embryologic studies, and the use of this term tends to cause confusion in the study of the tumors according to the outline that they themselves originally suggested. Such a change in terms should not be accepted unless it definitely clarifies one's conception of the tumor. Unless care is exercised, neurologists will tend to give their own favorite names to each tumor, and, like the workers in the Tower of Babel, will cease to speak the same language."

After all, Dr. Deery and I understand each other; we know what tumor we are talking about. Regarding this attempt at classification, I think that Dr. Deery has done well in attempting it. As Dr. Globus says, it is a question of whether it is of academic or of practical value. Dr. Deery has certainly given a great deal of time and study to this, and I congratulate him on the effort he has made. However, when he takes the various maturation levels as his basis, it must be

said in addition that these tumors are of tremendous complexity, and that many variations in cell types are found in a given case. These growths have been spoken of as benign and yet later on, after operation, they prove to be spongioblastomas in all their malignancy.

As to the duration of life, may I stress our uncertain position? In regard to the clinical history of a tumor of the brain, frequently in the very early history symptoms are mentioned which one would never ascribe to a tumor. There may be a history of some vertigo or of some headache for eighteen months previously, but if operation or autopsy did not reveal a tumor, the symptom of vertigo or headache might have been ascribed to any other cause. Unless the early symptoms continually persist up to the time when a diagnosis of tumor is definitely established, early complaints may be misleading. In other words, Dr. Deery did not say what early symptoms he used as criteria. One is therefore hampered in evaluating the early symptoms. In order to make this correlation, it seems to me that Dr. Deery must select certain symptoms which he can say must be symptoms characteristic of intracranial growth. If he can do that and establish a correlation with the time from the first symptoms to the time of operative intervention, then possibly he can come to a classification of these tumors.

DR. HENRY ALSOP RILEY: I do not wish to engage in any particular controversy with Dr. Strauss and Dr. Globus, and neither do I wish to involve myself in histologic details and nomenclature with which I am not intimately conversant, but I feel that the attitude displayed toward Dr. Deery's work is one of complacency with the earlier formulations, and one resistant to the introduction of what may possibly be a new and valuable idea. I can see no particular quarrel with the term "glioblastoma." Certainly the division of the word is not "glia" and "blastoma," but "glioblast" and the termination significant of tumor, so that I do not see that there is any particular objection to the term "glioblastoma" when it refers to a tumor which is derived from a glia cell. Why is there any particular sanction about the use of the term "spongioblastoma"? The term "spongio" as indicative of the origin of the cell is hallowed by usage, but it is not used at all in connection with the further development of that particular type of cell.

Dr. Strauss states that the symptoms which Dr. Deery mentioned may have been present from any cause, but these patients had a tumor of the brain. Of course, a great deal depends on the actual symptoms which Dr. Deery selects for his purpose, and such symptoms should be continuing ones. The presence of these symptoms cannot be casually ignored as being producible by any condition, as they appear in a patient in whom a tumor of the brain subsequently develops. One cannot lose sight of the fact that these patients did have a tumor of the brain, and therefore the symptoms may well have been associated with the early manifestations of the growth. I feel strongly that attempts to go more intimately into the nature and significance of these growths and their initial manifestations are well worth while.

DR. EDWIN M. DEERY: I am glad that Dr. Globus discussed the subject of nomenclature, as I know that most of us interested in the subject disapprove of changing the name of spongioblastoma multiforme. Personally, however, as will be understood, I felt in no position to disregard the request of the National Conference on Nomenclature of Disease.

Naturally, lacking a sufficiently long experience, I cannot attempt to answer the various major issues brought up by Dr. Globus and Dr. Strauss, and I was glad indeed to hear what they had to say. I think it is fair to mention again, however, that some of these patients gave a history of symptoms of two weeks' duration and others of six years. As far as I could, I chose definite symptoms pointing to a suggestion of intracranial involvement. To me it seems that somewhere there should be a histologic basis for such varying courses, and that is what I believed worth attempting to find.

Book Reviews

Phyloanalysis. By William Galt, M.A. Price, $1. Pp. 151. New York: Baker and Taylor Company, 1933.

This volume represents an attempt to give in outline certain aspects of the method of "phyloanalysis," developed by Dr. Trigant Burrow. The author takes pains to remind the reader that he cannot hope to obtain more than an idea as to the technic of phyloanalysis through reading this book, but that phyloanalysis is appreciable only in terms of actual participation in the subjective laboratory process of "group-analysis." The following is an effort to give the gist of the author's thoughts, some of which are not easy to follow.

Phyloanalysis is group-analysis, the group or phyletic method of behavior analysis. The process of phyloanalysis is primarily a study by oneself of reactions occurring within oneself under conditions of an experimental group set-up which permits the inclusion simultaneously of the reactions of others in a commonly controlled observation. The observer's own subjective material is brought to objective observation. He aims to attain an objective approach toward the subjective feelings and sensations offered for observation in the group of which he is a part. Group-analysis does not mean the collective psychoanalysis of a group of people, nor is it in any sense an application of the psychoanalytic method of Freud.

Group-analysis has to do with the physiologic reactions of man as they are expressed subjectively or in the sphere of his own feeling. It deals with reactions felt, not with reactions looked at through the employment of the projective senses. The prevailing "normal" social structure is held not to be basic or fundamental in nature, but on the contrary to represent a secondary and substitutive fabric which, like the fabrications of the neurotic person, is without direct biologic or organic foundation. The present social order, it is stated, is in large measure built on proprietary thought processes within each of us which do not rest on a biologic matrix embodying the phyletic experience of the species as a whole. These processes are constructed rather on the arbitrary mental concept or social image which each person holds privately in respect to himself and to others. The interposition of this social image places an insuperable obstacle between the observer and his object. In the findings of the laboratory of phyloanalysis this anomalous position of "stand-offness" and reference, which each person habitually assumes toward himself and others of his kind, has its biologic explanation in a phyletic or racial deflection of attention. This habit of deflection is such that it diverts the integral or organic attention of man from its function (and interfunction) as an intrinsic social process, and as a result man's interest is transferred, instead, to a disproportionate engrossment in his external appearance or surface behavior. Therefore, to apply this habitual projective mechanism of attention to the subjective field involves a deflection of the organism's primary, integral attention. It is to try to look out on or to see symbolically, or with the external senses, that which is within the organism and perceptible only organically.

The sole purpose of "researches in phylopathology" is to discover the causative factors responsible for distortions in the feeling life of man—distortions which in their individual expression take the form of neurosis and crime and which are represented in the community in such manifestations as war and other social catastrophes. There is no attempt to treat these conditions, individual or social, but merely to isolate and to establish the inciting causes of them. Group-analysis makes plain that the affect-logic beneath the manifest "cause" commonly assigned by normality is imaginal, that the whole social concept of cause and effect as it bears on the mental and emotional spheres of human conduct is arbitrary, pro-

jective and fanciful. The clinically insane personality is merely the person who has carried the mechanism of social divergence of attention to its ultimate and logical conclusion through recourse to private and segregated feeling evaluations. The feelings which now occupy the mental or projective sphere represent the merely substitutive image of fitness expressed in the socially projected symbol that only appears as outer goodness or rightness. Man's intellectual formulations as conveyed by the symbol, no matter how adroit, how brilliant, will never avail in extricating him from the organic dilemma in which he finds himself today. The purpose of the phyloanalytic experiment was that of divorcing from the concept or symbol the entire sum or system of affect-impressions now attaching to them and to allow such dislodged affects to be dissolved and reabsorbed into the total system in the form of unbiased feeling. The feelings that belong to the organism as a totality are an expression of the organism's inherent health or behavior fitness.

Readers of this review are in a position to judge for themselves the validity of the basic assumptions and formulations of what is called phyloanalysis. The method of science, of course, requires that, instead of speculating, one looks at, dissects and studies the subject matter of investigation as it presents itself. To evaluate and assign bases to man's social concepts, thought processes, feelings, symbols and intellectual formulations, without careful and painstaking observation and analysis of man's mental processes, is to the reviewer an arbitrary, speculative approach.

Die spezielle Chirurgie der Gehirnkrankheiten. Volume II. Parts 1 and 2. (Volumes 49a and 49b of Neue deutsche Chirurgie). Die epileptischen Erkrankungen. By Prof. Fedor Krause and Dr. Heinrich Schum. Price, 81 and 65.50 marks. Pp. 520 and 523. Stuttgart: Ferdinand Enke, 1931 and 1932.

In a previous issue there appeared a review of the first volume of "The Special Surgery of Diseases of the Brain." The first volume was under the general supervision of Prof. Fedor Krause, and the subjects were of general interest. The volumes here reviewed (volumes 49a and 49b) make up the second volume of this series. They are divided into two parts for convenience and are under the general editorial direction of Prof. Fedor Krause and Dr. Heinrich Schum. Volume 49a appeared in 1931 and volume 49b in 1932. Both are devoted to epileptic diseases. The subject is divided into ten special divisions. The first deals with the historical aspect, the second with statistical considerations, and the third with symptomatology, which takes up about 100 pages and is subdivided into two parts, the first being a description of the attacks and the second the course of the disease. The fourth division considers the subject of etiology, the fifth pathologic anatomy and the sixth physiologic considerations. Each of these divisions is subdivided according to the parts discussed. These are all in volume 49a.

Volume 49b contains the seventh to the tenth divisions, inclusive. The seventh concerns itself with the diagnostic measures, the eighth with operative considerations. This is a very large division; it is divided into two parts and takes up about 300 pages. The ninth division considers medicinal treatment, and the tenth discusses social considerations.

Obviously it would be difficult to review adequately such an enormous amount of work. It can be said, however, that it is very well done; the illustrations are excellent. It represents the strictly Germanic point of view, and as such it is a welcome addition to the knowledge of the subject of epilepsy.

Les tumeurs du quatrième ventricule. By J. Lereboullet. Price, 65 francs. Pp. 427. Paris: J. B. Baillière et fils, 1932.

This monograph is a scholarly and complete compilation of the literature on tumors of the fourth ventricle, together with the histories in twenty-five cases in

which autopsy was performed. It is more a reference work than an original contribution, and indeed few facts are brought forward which are not familiar to most neurologists. Much space is given to a review of the work of Cushing and his associates, which has drawn particular attention to the subject of tumors in the posterior fossa in the United States.

A tumor should be suspected when a patient under 20 years of age presents symptoms of increased intracranial pressure, and especially vomiting, vertigo and difficulty in walking. In young patients papilledema may be absent, but hydrocephalus may often be demonstrated by roentgen examination. Abnormal attitudes of the head are also suggestive, and tonic fits are extremely characteristic. There are, of course, cerebellar manifestations and palsies of the cranial nerves in many cases. The author states that lumbar puncture is dangerous in this condition, but reports sixty-three cases in which it was practiced; in four of the cases the author thought that serious symptoms were precipitated. A great variety of types of tumors may be encountered in the fourth ventricle, and it is usually impossible to make a pathologic diagnosis before operation. The cerebellum should be explored promptly when the diagnosis is made, and radiotherapy should not be used except after a suboccipital decompression.

Studies in the Dynamics of Behavior. By Calvin P. Stone, Chester W. Darrow, Carney Landis and Lena L. Heath. Edited by Karl S. Lashley. Price, $5. Pp. 331. Chicago: University of Chicago Press, 1932.

There are three sections in this study of separate significance, but all are units of a definite program of research to evaluate methods for measuring individual differences in emotional behavior. The first section is a laboratory study of "Wildness and Savageness in Rats," made on both wild and tame stock. The second section, "Reaction Tendencies in Personality," is largely a physiologic study correlated with questionnaire data as to the subject of personality and subjective reactions. The authors believe that any correlations between personality traits and physiologic reactions are not unimportant. This study makes definite steps toward closer connections between laboratory experiments and personality reactions, but the authors modestly refrain from any claims other than that they find evidence of probable significance of the various physiologic measures for personality.

The last section, "Measuring Traits in Delinquency," is really a laboratory study endeavoring to evaluate carefully present well known methods or special tests in regard to their accuracy, and dealing with measurement of objectification of emotional or psychopathic traits. The conclusions in this section contain the comment that in general (from the laboratory standpoint) analytic investigations of personality traits, of emotionality or of psychopathy are unsatisfactory and fail to bring out decisive evidence.

These studies represent splendid work of a conservative and scientific type. All psychologists or experimenters in any field should become familiar with this work. It is highly technical, and contains many charts, graphs, tables and compilations of various sorts. For this reason it is of little interest to the clinician, but will be a reference of great value to research workers.

Case Studies in the Psychopathology of Crime. By Ben Karpman. Price, $12. Pp. 1,042. Washington, D. C.: Mimeoform Press, 1933.

It is well known that case histories in psychiatric papers and books do not make easy reading. This enormous volume of more than a thousand pages is entirely composed of five extremely extensive histories of criminals. It is apparent, therefore, that it is a book which is difficult and somewhat cumbersome to read. For the psychiatrist interested in crime there is, however, a great deal of interest in these pages—not so much perhaps with respect to the psychology or psychopathology of these individual criminals, as with respect to the detailed descriptions of the milieu through which they move. Those unfamiliar with the administration of justice to criminals can learn from this book a great deal of the well nigh

incredible degradation of human beings in jail. A full evaluation of the more strictly psychopathologic aspect of the book had better be postponed until the parallel volume appears. It is announced by the author under the title "The Individual Criminal." It is planned for the early future and will concern itself "with an intimate psychogenetic discussion of the material."

The Tides of Life: The Endocrine Glands in Bodily Adjustment. By R. G. Hoskins. Price, $3.50. Pp. 348. New York: W. W. Norton & Company, Inc.

This book contains a well written popularization of generally accepted facts of endocrinology. It is intended to interest the lay reader, and no attempt has been made to present new facts or even to cover the ground thoroughly. Considerable space is devoted to simplified explanations of anatomy and physiology. It is, however, up to date, and most physicians will find it profitable reading for the bird's eye view which it affords of the amazing developments of recent years in the physiology of the ductless glands. In general, a fairly critical point of view is maintained toward the material presented—far more critical than that found in most systems of endocrinology of scientific pretentions. The weakest chapter is doubtless that on the pituitary gland, in which the Laurence-Biedl syndrome is assumed to be of pituitary origin, and the efficacy of the treatment of dwarfism with material from the anterior lobe is implied. The fantasies of some fervent endocrinologists, such as Berman, are quoted with a smile, but somewhat similar statements by others such as Timme and Rowe are accepted at their face value. The style is readable and entertaining.

Les syndromes hypophysaires et infundibulo-tubériens. By Antoine Raybaud. Price, 25 francs. Pp. 64, with 14 illustrations. Paris: Gaston Doin & Cie, 1933.

This book is one of a long series of monographs, not all of which have as yet appeared. It forms a part of a series, "La pratique médicale illustrée," which deals with present-day aspects of practical medicine. Each monograph is to be about fifty pages long. The subject is discussed under six main headings: (1) anatomy and physiology, (2) classification of syndromes, (3) clinical descriptions of syndromes, (4) progress of pituitary syndromes, (5) diagnosis and (6) treatment. Subjects such as gigantism, hypophyseal infantilism, nanism and neurovisceral syndromes are discussed.

The author has covered the subject well, considering the restrictions in length. Many references are made to the literature, but the actual citations are not given; the illustrations are not adequate. These omissions interfere with the value of the work, for it adds little for those who know the subject reasonably well and does not give sufficient illustrations of patients for those who do not know it well.

The Harvey Lectures. Delivered Under the Auspices of the Harvey Society of New York, 1931-1932. Series XXVII. Price, $4. Pp. 226. Baltimore: Williams & Wilkins Company, 1932.

The Harvey Lectures, which are given under the auspices of the Harvey Society, have since 1903 occupied a very important position, for practically all of the lectures given have been delivered by men of international reputation and on topics in which the lecturers have been distinguished. The twenty-seventh series of lectures bears tribute to this. From the neurologic standpoint, Dr. E. D. Adrian, the winner of this year's Nobel Prize in Medicine, lectured on "The Messages in Sensory Nerve Fibres." This work has been published under the guidance of Graham Lusk, who died on July 18, 1932. Like most successful societies, it was entirely due to the work of one man, in this instance, Dr. Lusk.

Die Einteilung des Nervensystems nach seinen Leistungen. By L. R. Müller. Price, 6.80 marks. Pp. 74. Leipzig: Georg Thieme, 1933.

In this interesting presentation the author divides his material into three general divisions. The first deals with the reactions of the nervous system to the surroundings (*Systema pro mundo*), the second with the relationship of muscle tone and postures of the body (*Systema nervorum myotonicum et myostaticum*) and the third with what the author terms the vital nervous system (*Systema nervorum vitale*), dealing with the autonomic systems which regulate visceral function and other primitive activities. The last part is particularly interesting and in many respects presents new points of view. The illustrations are excellent, and the book is worth reading.

A Point Scale of Performance Tests. Volume II. The Process of Standardization. By Grace Arthur. Price, $1.50. Pp. 106. New York: Commonwealth Fund, 1933.

This volume supplements the author's "Clinical Manual," in which she presented her scale, which included many of the most useful performance tests, and her method of rating. The new publication describes the procedures by which the point scale was developed, and gives the statistical data. It will be of value to those who are using the point scale and, in addition, to those interested in the construction and standardization of intelligence tests.

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